STUDIES ON THE CHEMISTRY OF QUINOXALINES AND BENZIMIDAZOLES

by

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To Janet

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Summary

A number of quinoxalinium perchlorates have been prepared by the reaction of the corresponding quinoxalinone N-oxide with acetic anhydride in the presence of perchloric acid. The reactions of these quinoxalinium perchlorates with nucleophiles have been investigated. With anions (acetate, chloride, thiocyanate and hydroxide ion), the quinoxalinium perchlorates gave 7-substituted quinoxalinones. The facility with which the quinoxalinium perchlorates undergo nucleophilic substitution is demonstrated by the reaction of 4-N-acetoxy-6-chloro-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalinium perchlorate with water to give 6-chloro-7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one. The quinoxalinium perchlorates also react in general with alcohols to give 7-alkoxy derivatives. The reactions of the quinoxalinium perchlorates with amines have also been studied. In some cases reaction with diethylamine gives 7-diethylamino quinoxalinone derivatives. In other cases, reaction with morpholine or diethylamine gives intermediate quinoxalinone adducts. The structures and transformations of these adducts support the mechanism suggested for the reaction of the quinoxalinium perchlorates with nucleophiles.

A number of 2-nitroanilinoacetonitriles have been prepared by the reaction of 2-nitroanilines with formaldehyde and sodium cyanide in the presence of zinc chloride. The 2-nitroanilinoacetonitriles undergo base-catalysed cyclisation providing a synthetic route to 2-cyano-1-hydroxybenzimidazoles. This type of cyclisation was extended to α-substituted 2-nitroanilinoacetonitriles. α-(2-Nitroanilino)phenylacetonitrile undergoes base-catalysed

cyclisation to give 1-hydroxy-2-phenylbenzimidazole. However, the attempted cyclisation of α-(2-nitroanilino)propionitrile was unsuccessful. On the other hand, the cyanomethylation of N-substituted 2-nitroanilines gives N-substituted 2-nitroanilino-acetonitriles which undergo base-catalysed cyclisation providing a general route to 1-hydroxybenzimidazolinones. The attempted reactions of N-substituted 2-nitroanilines with acetaldehyde or benzaldehyde and sodium cyanide in the presence of zinc chloride were unsuccessful. Reaction of the 1-hydroxybenzimidazolinones with acetic anhydride under mild conditions gives N-acetoxy derivatives which undergo rearrangement to 5-acetoxybenzimidazolinones when heated under reflux in toluene, ethanol or glacial acetic acid. The reactions of 1-hydroxybenzimidazolinones with hot acetic anhydride and acid chlorides (acetyl chloride, acetyl bromide, benzoyl chloride and toluene-p-sulphonyl chloride) lead to a variety of 5-substituted benzimidazolinones. The mechanisms of these reactions are discussed.

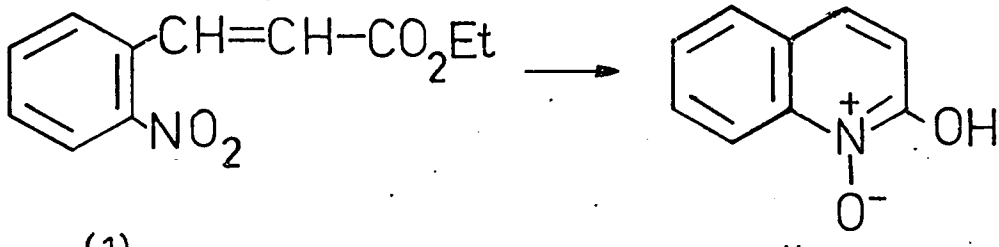
Contents

Chapter One

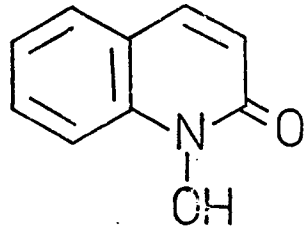
Introduction

1.1 Introduction

One of the earliest examples of the synthesis of a heterocyclic N-oxide was the preparation of "oxycarbostyril" in 1881 by Ostermaier and Friedländer[1], when studying the reduction of ethyl o-nitrocinnamate (1). "Oxycarbostyril" was later shown by Friedländer[2] to be carbostyril N-oxide (2). Meisenheimer[3] first prepared pyridine N-oxide by perbenzoic acid oxidation of pyridine



(1)

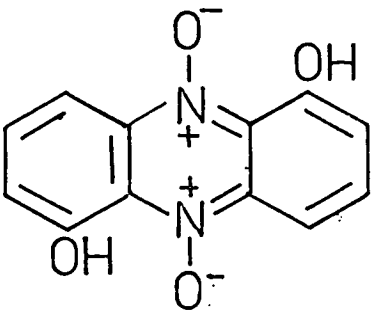


(2)

in 1926. The number of N-oxides which were synthesised increased steadily and by the end of the 1930's they were a well recognised group of compounds.

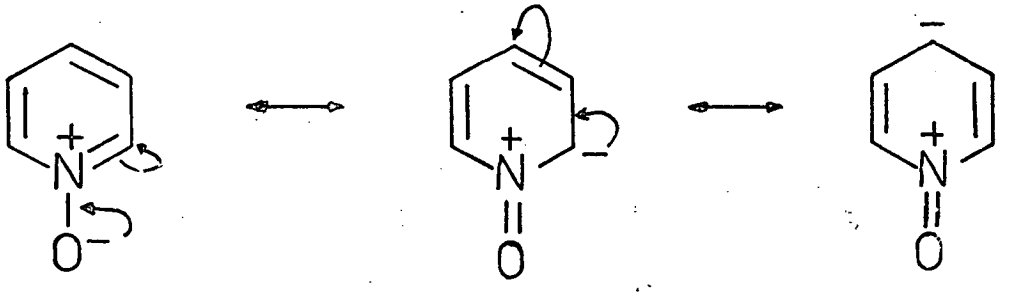
Interest in the chemistry of heterocyclic N-oxides was enhanced by the discovery that certain biologically active natural products contained the N-oxide functional group [e.g. the antibiotic iodinin[4] (1,6-dihydroxyphenazine N,N-dioxide) (3)].

A more important development in the chemistry of heterocyclic N-oxides was the observation by Linton[5] that the dipole moment of



(3)

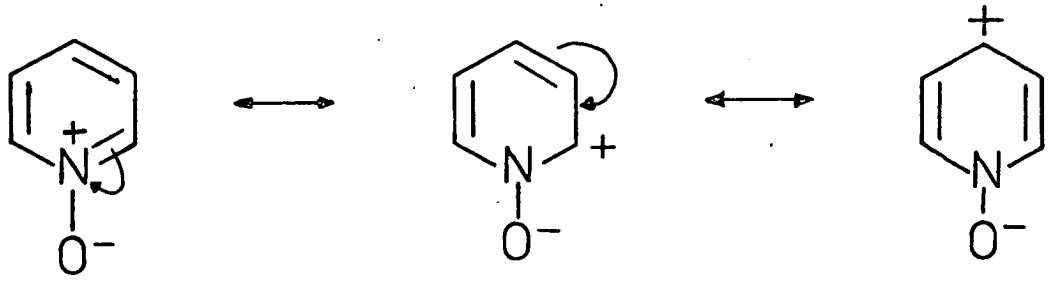
pyridine N-oxide (4) was much lower than expected. He concluded that this was due to conjugation of the negatively charged oxygen atom with the π-electrons of the aromatic ring (4). The shift of electrons from the oxygen atom to the aromatic ring partially cancels the dipole moment of the N-oxide group. This indicated that the canonical forms (5) and (6) must make a significant contribution to the resonance hybrid. This work led Ochiai to predict



(4) (5) (6)

that electrophilic substitution in pyridine N-oxide would take place in the 4-position[6] and this he also proved experimentally.

The resonance structures (7) and (8) also contribute to the resonance hybrid due to polarisation in the opposite direction. Katritzky has shown this by comparison of the dipole moment of pyridine with those of γ-substituted pyridines[7]. He showed that



(4) (7) (8)

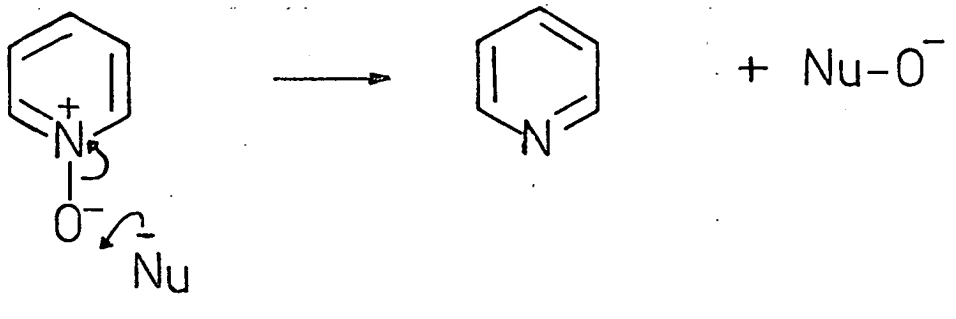
the difference between the dipole moments of pyridine and pyridine N-oxide was increased by electron donating groups and decreased by electron withdrawing groups in the δ-position. This indicated that the electronic shift shown by the curved arrow in resonance structure (7) was greater in pyridine N-oxide than in pyridine.

The fact that the N-oxide group is polarised in both directions accounts for the great variety in the reactions of heterocyclic N-oxides and is responsible for the fact that heterocyclic N-oxides can react with both nucleophiles and electrophiles. Since the experimental section of this thesis deals with nucleophilic attack on N-oxygenated heterocycles, only the reactions of heterocyclic N-oxides with nucleophiles will be discussed in detail in this introduction.

1.2 Reactions of Heterocyclic N-Oxides with Nucleophiles

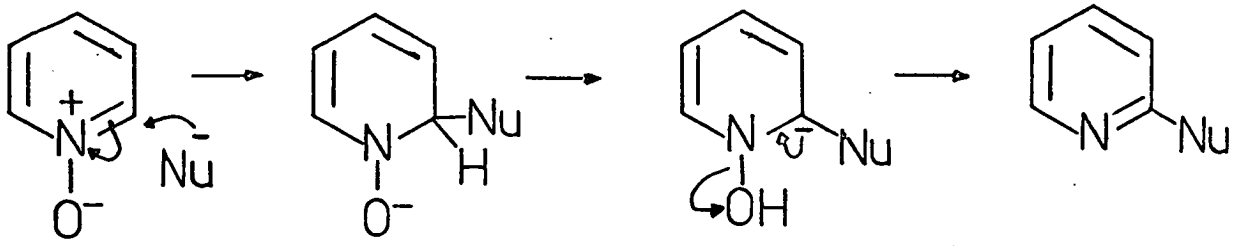
Heterocyclic N-oxides can undergo nucleophilic attack in two ways:-

(a) At the N-oxide group



(9) (10)

(b) At the ring



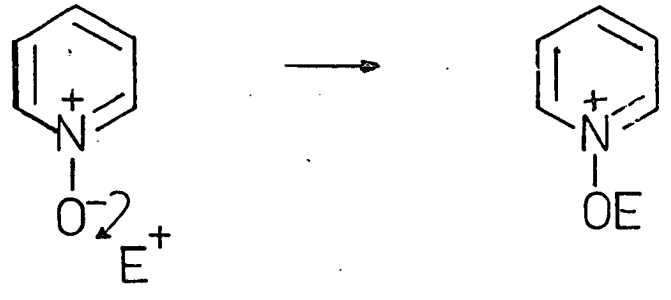
(11) (12) (13) (14)

(a) Reactions Involving Nucleophilic Attack at Oxygen

An Example of nucleophilic attack at the N-oxide oxygen atom is deoxygenation of heterocyclic N-oxides (9 → 10) to the parent heterocycle. This is the simplest type of reaction between a heterocyclic N-oxide and a nucleophile. Reagents which can be used for this reaction include phosphorus trihalides and trialkyl and triarylphosphite esters.

(b) Reaction Involving Nucleophilic Attack On the Ring

It should be noted that many reactions involving nucleophilic attack at a ring carbon atom occur by preliminary co-ordination between the oxygen atom of the N-oxide and an electrophile. Electrophilic reagents react with heterocyclic N-oxides to give



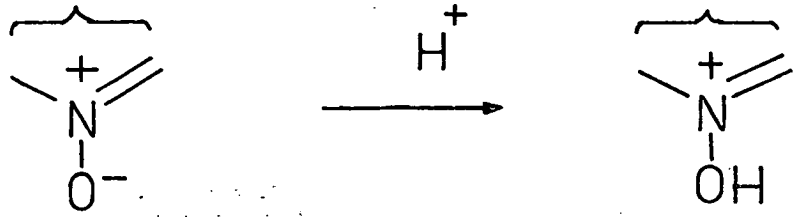
(15) (16)

adducts (15 → 16) which may be stable or which may undergo subsequent reaction depending on the reagent and the reaction conditions used.

Such electrophilic attack at oxygen is exemplified by:-

(i) Addition of a proton

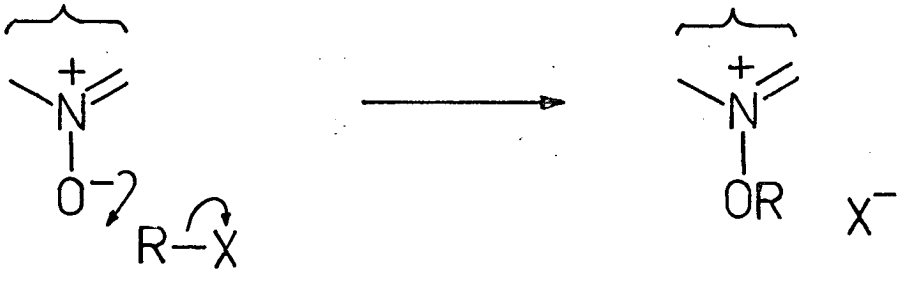
Heterocyclic N-oxides are weakly basic and form salts with strong acids (17 → 18)



(17) (18)

(ii) O-Alkylation of N-Oxides

Heterocyclic N-oxides react with halogen compounds to give quaternary salts which are usually very reactive and can seldom be isolated. However, the salts derived from alkyl halides (19 → 20) and sulphonates are isolable. These quaternary salts (20) can often be isolated as their perchlorates[8]. Formation of the salts

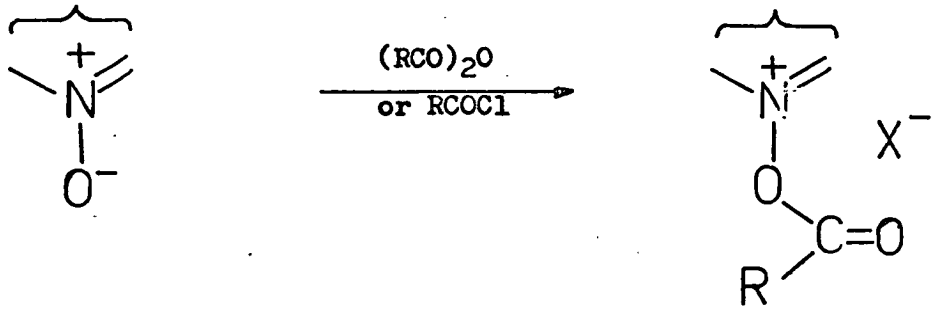


(19) (20)

(20) is sterically hindered by substituents in the α-position and is electronically inhibited by electron withdrawing substituents in the β - or γ-positions of the ring.

(iii) O-Acylation of N-Oxides

N-Oxides react with acylating agents to form N-acyloxy quaternary salts (21 → 22). The N-acyloxy quaternary salts (22) are very reactive and are somewhat difficult to isolate. However,



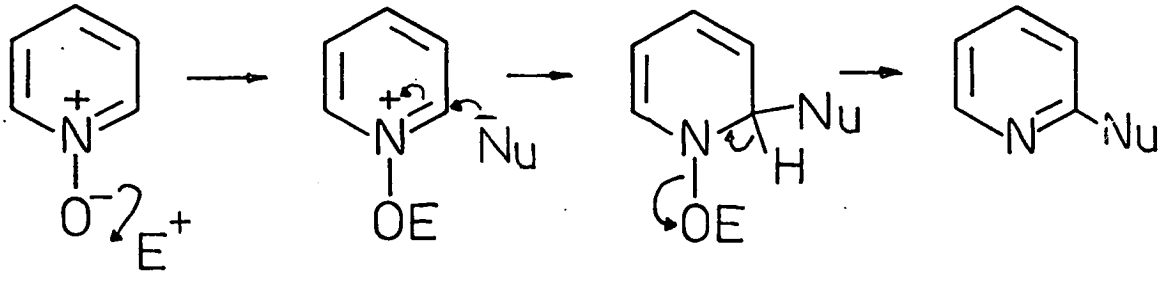
(21) (22)

[X = RCO_2 or Cl]

the use of the poorly nucleophilic perchlorate ion as the counterion in these salts has a stabilising influence and Traynelis[9] has reported the isolation of a series of 1-acetoxypyridinium perchlorates. Relatively stable 1-acyloxypyridinium perchlorates have also been prepared by Muth and Darlak[10]. Quinoline N-oxides are also reported to form relatively stable N-acetoxy perchlorates[10, 11, 12].

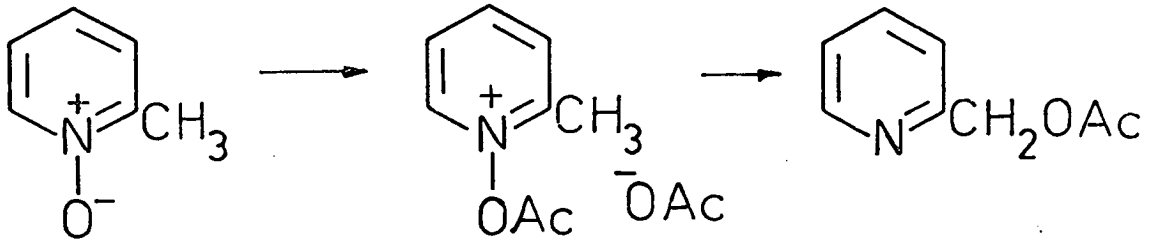
As discussed earlier, the presence of a positively charged nitrogen atom in the ring in heterocyclic N-oxides causes polarisation of the ring π-electrons towards the nitrogen atom and consequently, heterocyclic N-oxides can undergo nucleophilic attack at the position α and γ to the N-oxide group [cf. (4) ↔ (7) ↔ (8)]. Normally only the strongest nucleophiles (eg. carbanions derived from organometallic reagents) can attack an unactivated ring containing an N-oxide group (11 → 14). More commonly, nucleophilic attack is preceded by co-ordination by an electrophilic species at the N-oxide oxygen (15 → 16) followed by nucleophilic addition

(16→23). Elimination (23→14) then gives the final product.



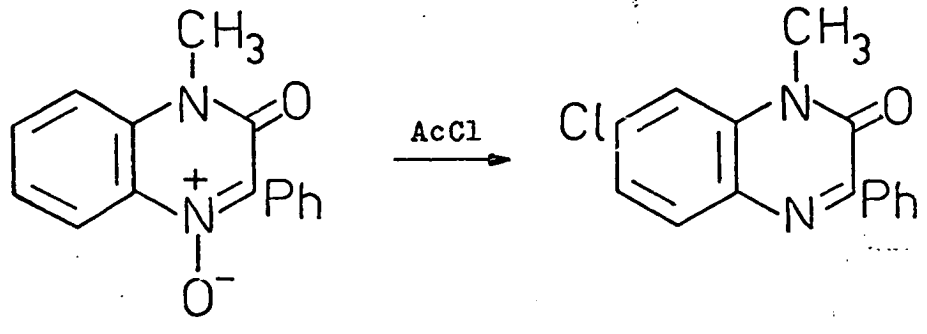
(15) (16) (23) (14)

Reactions of this type usually result in the formation of an α- or γ-substituted heterocycle (15→14) but rearrangements can also occur (24→26).[13] In general, nucleophilic attack takes place at



(24) (25) (26)

the α-position but if this is blocked, attack can occur at the γ-position. If both the α- and γ-positions on the heterocyclic ring are blocked, attack can occur on a fused benzene ring, e.g. 1-methyl-3-phenylquinoxalin-2(1H)-one 4-N-oxide (27) when heated under reflux with acetyl chloride in acetic acid gives 7-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (28).[14]

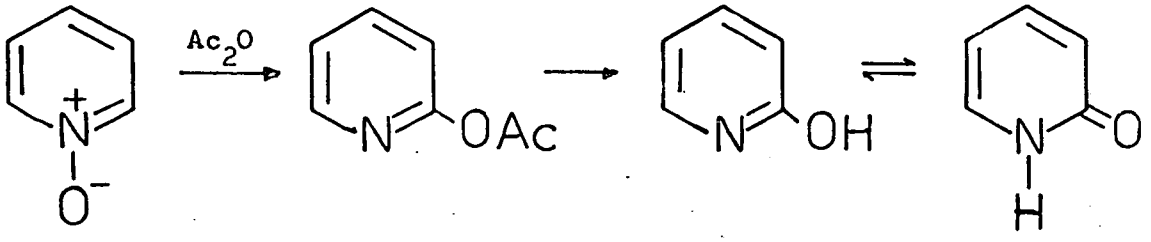


(27) (28)

Nucleophilic substitution reactions of heterocyclic N-oxides are exemplified by:-

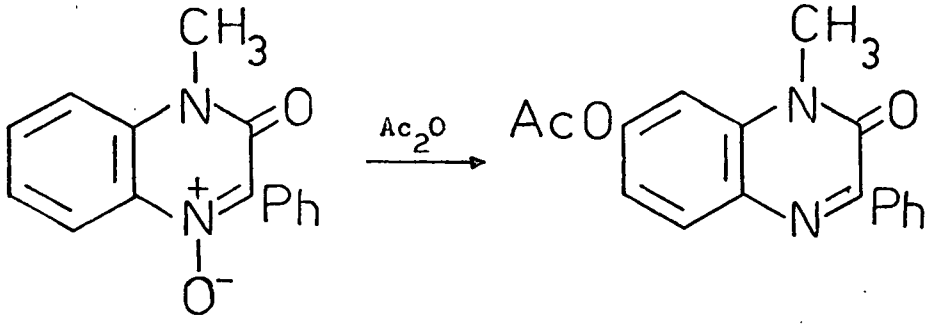
1.3 Reaction with Acetic Anhydride

The first reaction of a heterocyclic N-oxide with an acylating agent was carried out by Katada[15] who reported that pyridine N-oxide (4) when treated with acetic anhydride gave 2-acetoxy-pyridine (29) which was hydrolysed in the course of the work up to give 2-pyridone (31). In this type of nucleophilic substitution,

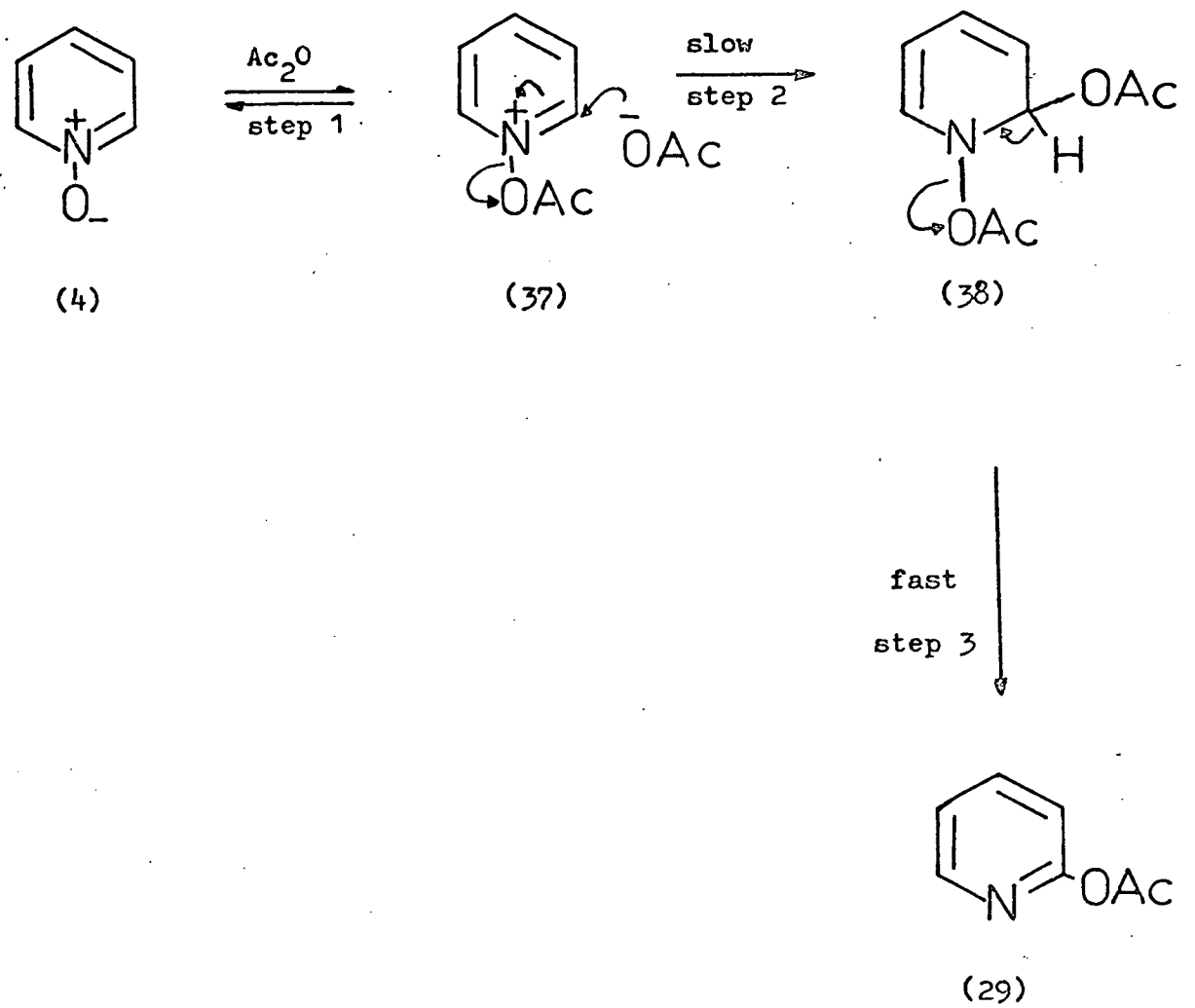


(4) (29) (30) (31)

if both the α-positions are blocked, substitution can take place at the γ-position. However, if a methyl group is present in the α-position, rearrangement can occur (24 → 26)[13]. In a benz-fused heterocyclic N-oxide where the α- and γ-positions are blocked, the acetoxy group is introduced into the benzene ring. Thus 1-methyl-3-phenylquinoxalin-2(1H)-one 4-N-oxide (27) when treated with hot acetic anhydride yields 7-acetoxy-1-methyl-3-phenyl-quinoxalin-2(1H)-one (32)[14]. Benzimidazole 1-oxide (33) likewise



(27) (32)

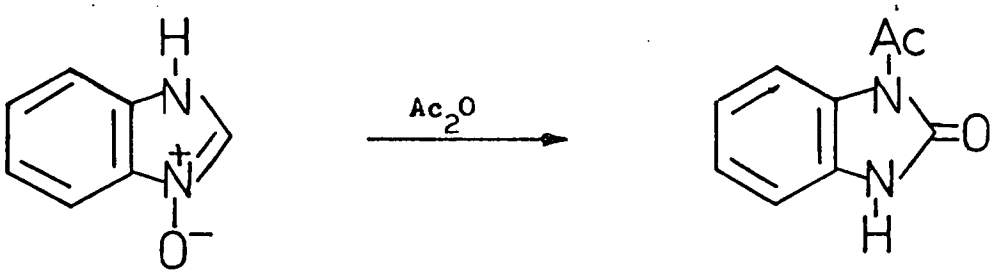


(4) (37) (38)

(29)

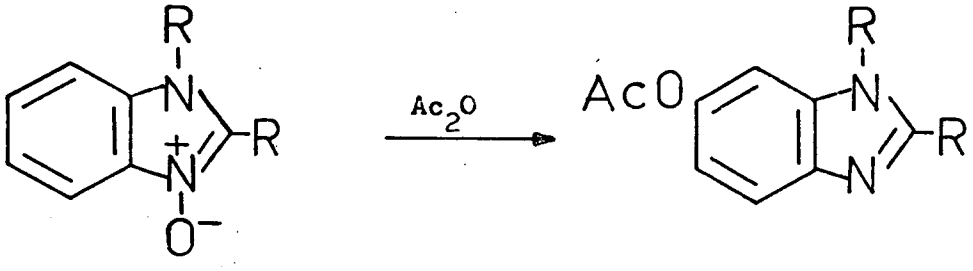
scheme 1

reacts with acetic anhydride at room temperature to give 3-acetylbenzimidazolin-2-one (34)[16], whereas 2,3-disubstituted



(33) (34)

benzimidazole 1-oxides (35) react with acetic anhydride to give 5-acetoxybenzimidazoles[17](36).

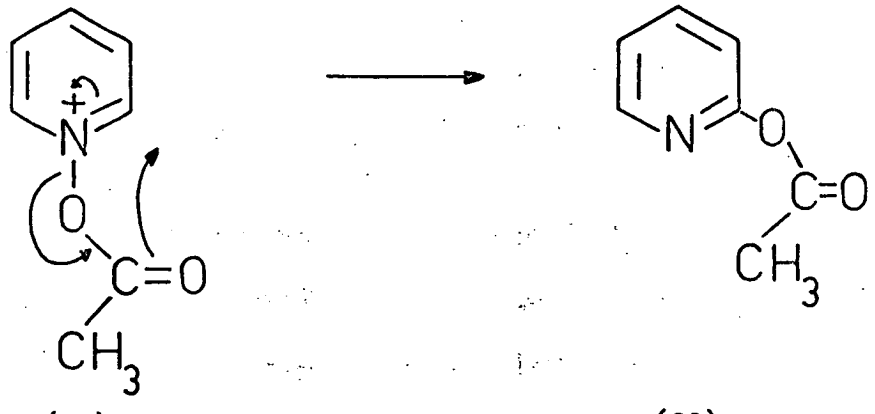


(35) (36)

The ionic mechanism which has been proposed[18,19,20] for the reaction of pyridine 1-oxide (4) with acetic anhydride is outlined in scheme 1. The initial step in the reaction (step 1, scheme 1) is electrophilic attack by the acetic anhydride at the N-oxide oxygen to produce the 1-acetoxypyridinium acetate (37) (*cf.* 15 → 16) which is in equilibrium with the N-oxide (4). The 1-acetoxypyridinium acetate (37) then undergoes nucleophilic attack by acetate ion (step 2, scheme 1) to give the intermediate (38) which loses the elements of acetic acid (step 3, scheme 1) to give the observed product (29).

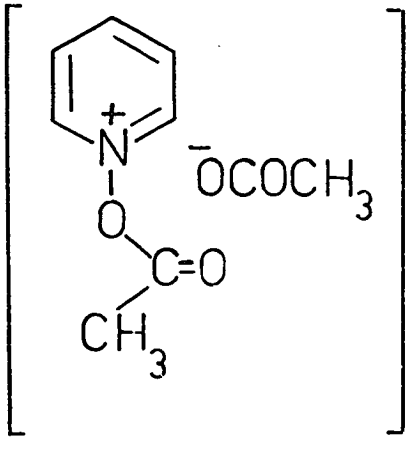
There is no direct evidence to support the equilibrium

(4 ⇌ 37) in the reaction of pyridine N-oxide with acetic anhydride but isotopic labelling studies of the reactions of 2-alkylpyridine N-oxides with acetic anhydride support the existence of such an equilibrium.[9] Markgraf[18] has investigated the kinetics of the reaction of pyridine N-oxide (4) with excess of acetic anhydride and found that the reaction exhibited pseudo first order kinetics. This is consistant with intermolecular nucleophilic addition of acetate ion to the cation (37) to give the adduct (38) being the rate determining step. Markgraf also excluded the intramolecular pathway for the rearrangement of the free cation (39 → 29) to the product because his kinetic data did not fit the rate expression for this process. Although Markgraf's work showed that the reaction

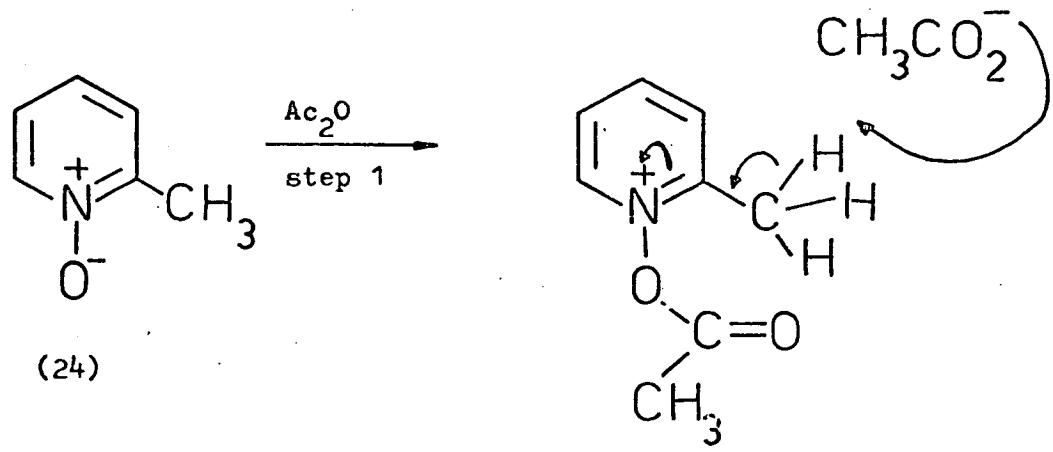


(39) (29)

was ionic, the kinetic evidence fails to distinguish between an intermolecular pathway (37 → 29) and one involving an intimate ion pair (40). These pathways can be distinguished by using isotopic

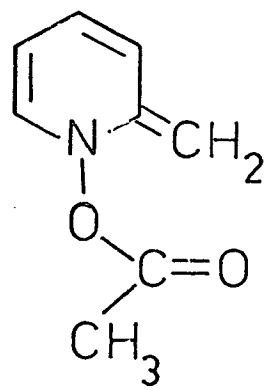


(40)



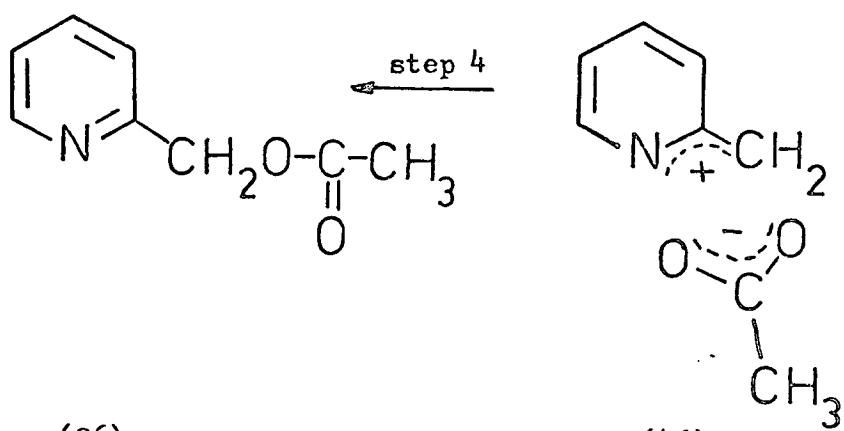
(24) (44)

step 2 $-H^+$



(45)

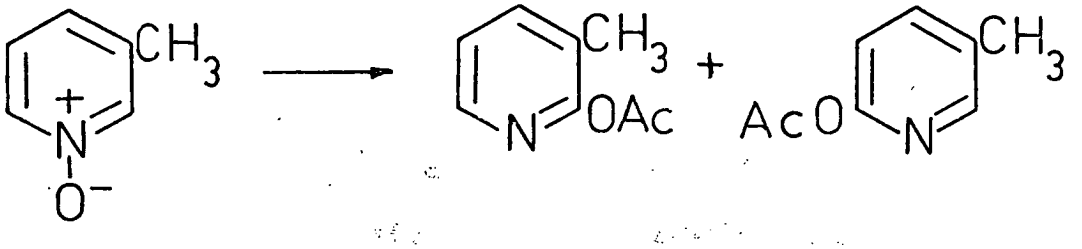
step 3



(26) (46)

scheme 2

labelling. Oae[19] has studied the reaction of 3-picoline N-oxide (41) (^{18}O = 0.20 atom %) with an equimolar amount of uniformly ^{18}O-labelled acetic anhydride (^{18}O = 0.89 atom %) and has found that the mixture of 2-acetoxy-3-methylpyridine (42) and 2-acetoxy-5--methylpyridine (43) contained 0.73 atom % ^{18}O. Control experiments

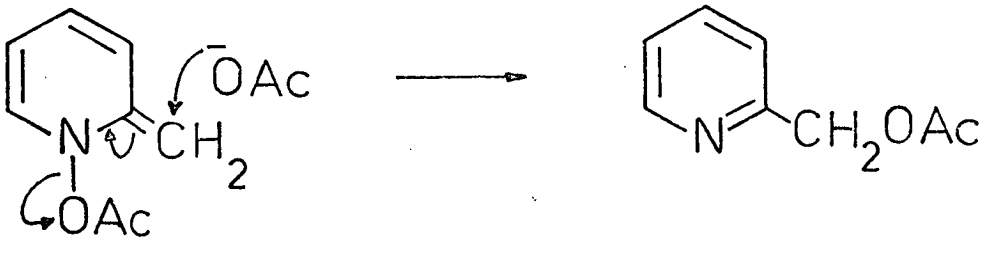


(41) (42) (43)

were carried out which excluded oxygen exchange of the acetoxy compound (42) with acetic anhydride or acetic acid. This complete oxygen scrambling is best explained by a mechanism involving an intermolecular process involving nucleophilic attack by acetate ion on an N-acetoxypyridinium cation (cf. step 2, scheme 1). Oae has also used this tracer technique to study the reaction of pyridine N-oxide (4) with ^{18}O-labelled acetic anhydride[20] and has confirmed Markgraf's result that the rate determining step for the reaction is addition of acetate ion at the 2-position of the N-acetoxy-pyridinium ion (37 → 38) (scheme 1).

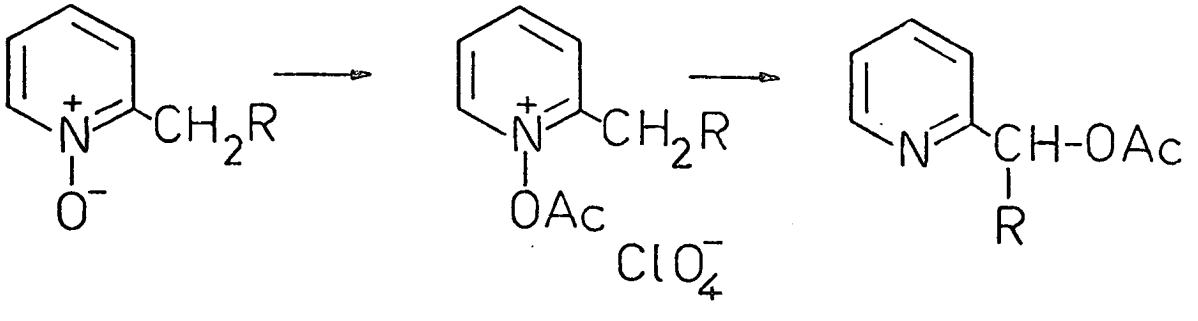
The reaction of 2-methylpyridine 1-oxide (24) with acetic anhydride to give 2-acetoxymethylpyridine (26) can be explained by a variation (scheme 2) of the ionic mechanism for the reaction of pyridine N-oxide with acetic anhydride. The initial step in the reaction (step 1, scheme 2) is again the formation of an N-acetoxy-pyridinium acetate (44) which in contrast to the pyridinium salt (37)

in scheme 1 can now eliminate a proton (step 2, scheme 2) to form the anhydro base (45). The N-O bond of the anhydro base (45) can then undergo heterolytic fission to give the intimate ion pair (46) (step 3, scheme 2). The final step (step 4, scheme 2) in the mechanism is recombination of the ion pair (46) to give the observed acetoxy compound (26). The process is an intramolecular rearrangement but is not fully concerted. The fully concerted cyclic rearrangement of the anhydro base (45) to the acetoxy compound (26) has been rejected by Oae[21,22] on the basis of his studies using ^{18}O-labelled acetic anhydride. It should be noted that the anhydro base (45) could theoretically undergo an <u>intermolecular</u> rearrangement (47 → 26) to give the observed product. Traynelis[9] in his work on the mechanism of the reaction of 2-alkylpyridine N-oxides (48) with

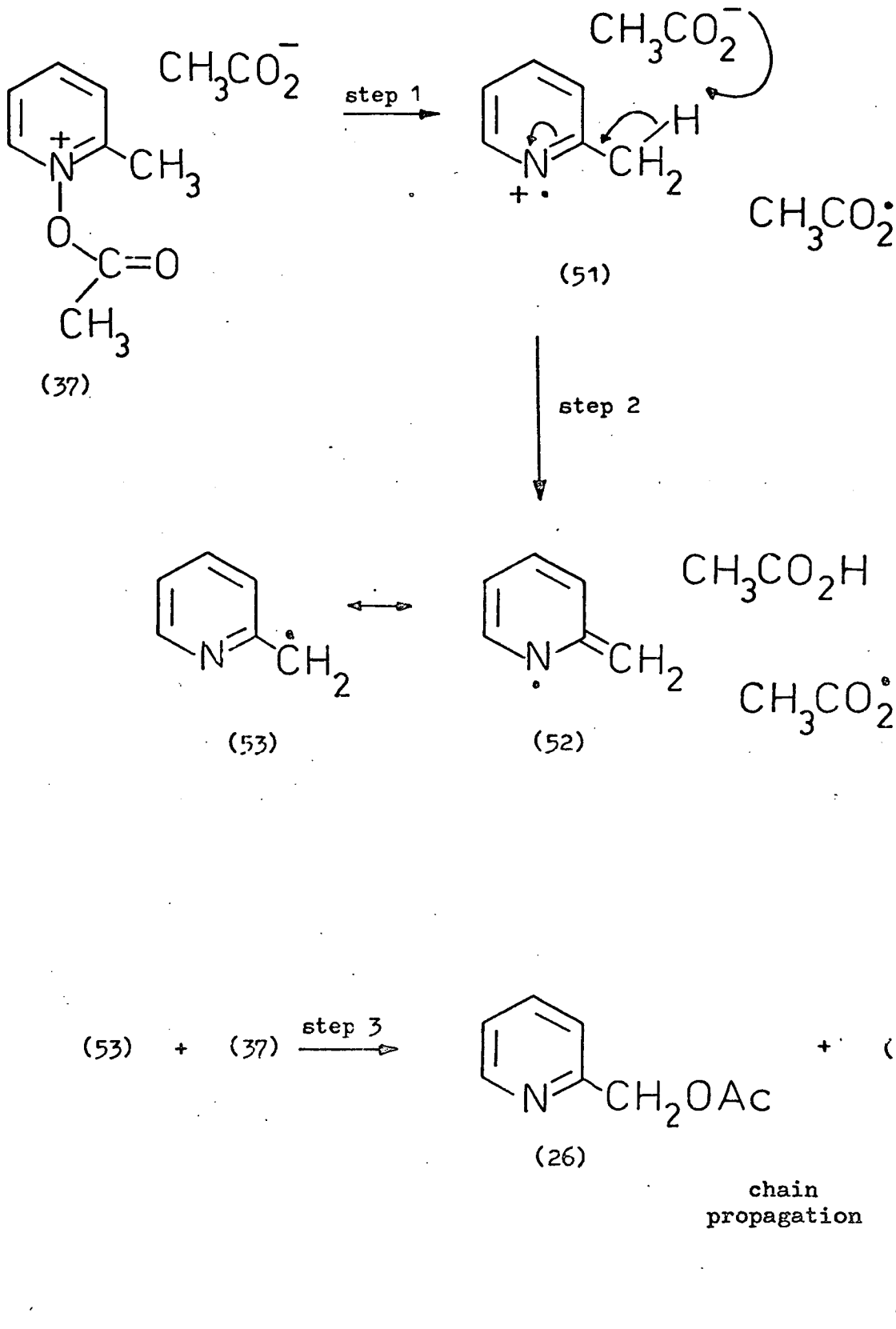


(47) (26)

acetic anhydride has isolated N-acetoxypyridinium cations as the perchlorates (49) and has observed that the conversion of these



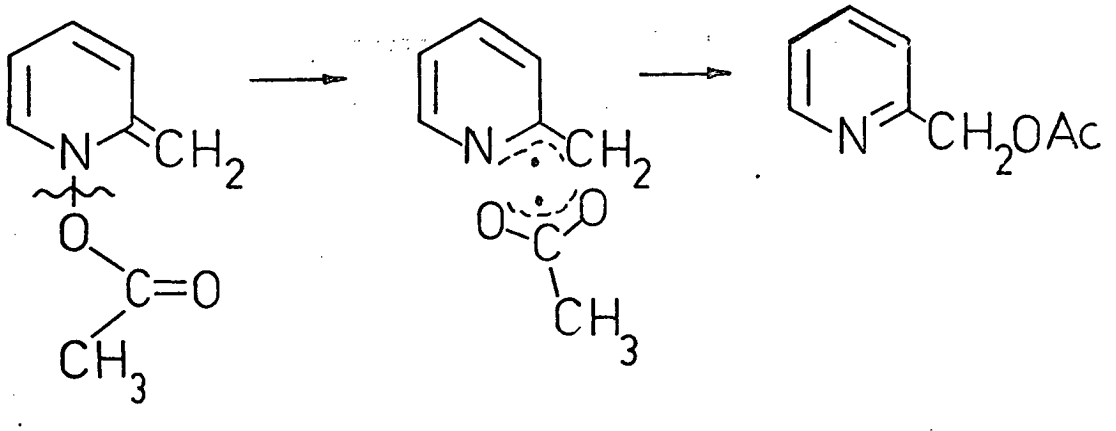
(48) (49) (50)


CH3CO2−
step 1
CH3CO2−
CH3
N+
O
C=O
CH3
(37)
H
CH2
N+•
CH3CO2•
(51)
step 2
CH2
N
CH2
N
CH3CO2H
CH3CO2•
(53)
(52)
(53) + (37)
step 3
CH2OAc
N
(26)
+ (51)
chain propagation

scheme 3

perchlorates (49) into the acetoxy derivatives (50) can be carried out by the use of a base such as triethylamine. This supports the proton abstraction stage (step 2, scheme 2) in the reaction mechanism. The intramolecular nature of the rearrangement (scheme 2) is supported by the fact that in experiments carried out in the presence of other ions[23] such as chloride ion, these ions were not incorporated into the product.

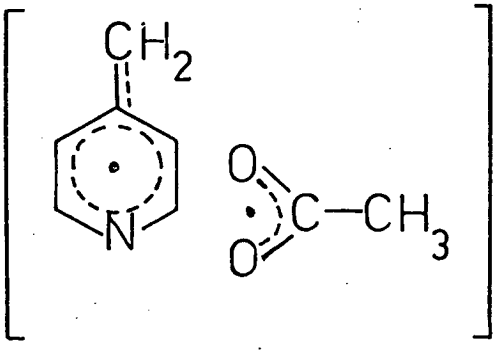
A radical mechanism[24] has also been suggested (scheme 3) to account for the reaction of 2-methylpyridine N-oxide (24) with acetic anhydride to give 2-acetoxymethylpyridine (26). In this radical mechanism, the N-acetoxypyridinium acetate (37) undergoes homolytic fission at the N-O bond producing a radical cation (51) which undergoes proton abstraction (step 2, scheme 3) to give the 2-picolyl radical (52 ↔ 53). This radical then reacts with the N-acetoxypyridinium acetate (37) (step 3, scheme 3) to produce the product (26) and regenerates the radical cation (51). Another possible radical mechanism involves homolytic fission of the N-O bond in the anhydro base (45) to give an intimate radical pair (54)



(45) (54) (26)

which undergoes an intramolecular rearrangement to form the observed product (26).

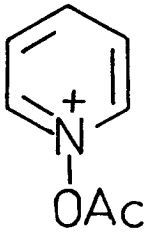
The presence of free radicals in the reaction mixture was demonstrated by Boekelheide[24] who showed that the introduction of styrene into the reaction mixture resulted in the formation of polystyrene. However, it was found that the addition of free radical inhibitors[25] to the reaction mixture stopped the formation of the polystyrene but had no effect on the yield of the 2-acetoxymethylpyridine (26). This observation excludes the radical chain mechanism for the reaction (scheme 3) but does not exclude the possibility that an intimate radical pair (54) is formed which is enclosed in a solvent cage and is unaffected by free radical inhibitors. Iwamura[26] has studied the reaction of 2-picoline N-oxide (24) with acetic anhydride in the hope of detecting CIDNP effects. Although acetoxyl radicals were observed in the reaction mixture no polarisation was observed throughout the reaction and he concluded that the rearrangement did not appear to proceed by a free radical ion pair. However, Iwamura has detected a CIDNP signal in the reaction of 4-picoline N-oxide with acetic anhydride and has cited this as direct evidence for the transient formation of the radical pair (55) in the reaction mixture[27].



(55)

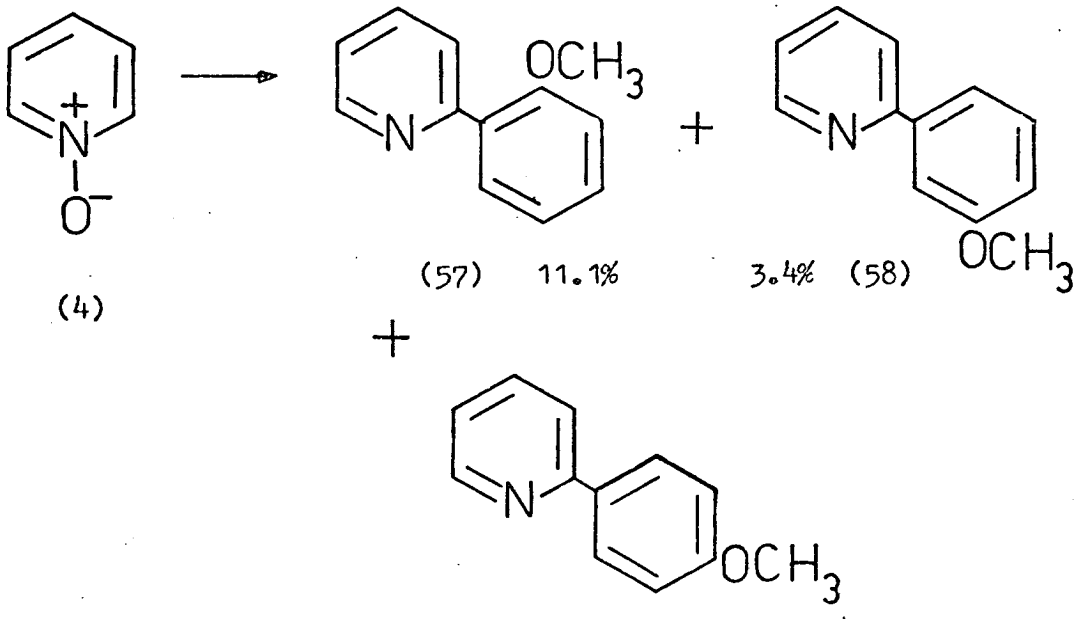
Evidence supporting the formation of the N-acetoxypyridinium cation (56) in the reaction of pyridine N-oxide (4) with acetic

anhydride has been obtained by Cohen and Deets[28] who carried out



(56)

the reaction in the presence of anisole and found that products derived from attack by the anisole at the 2-position of the pyridine ring were obtained (57-59). Since cations substitute into anisole predominantly at the ortho and para positions[29], the fact that the



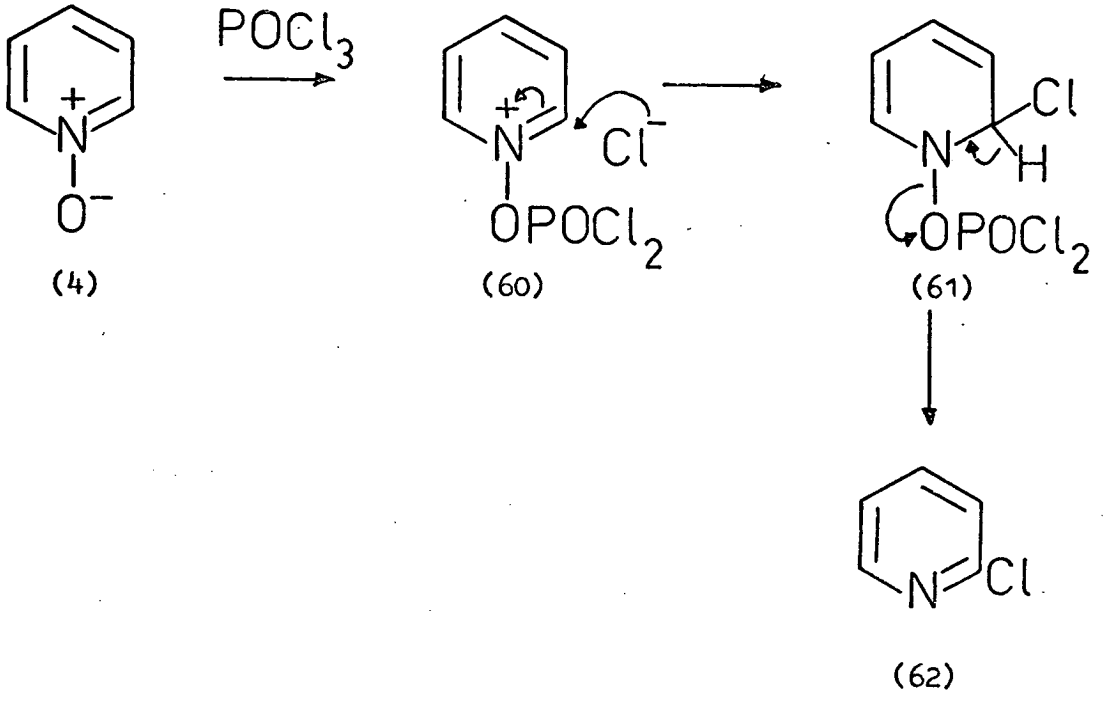
(4) (57) 11.1% 3.4% (58)

(59) 7.4%

ortho (57) and para (59) isomers predominated in the mixture was considered to be indicative of the existence of the cation (56) in the reaction mixture. Cohen has reported similar work in the reaction of 2- and 4-picoline N-oxide with acetic anhydride[30], which supports the formation of the ion pair (46) (step 3, scheme 2) in the reaction mechanism.

1.4 Chlorination Reactions

Heterocyclic N-oxides react with phosphorus oxychloride, phosphorus pentachloride or sulphuryl chloride to give chlorinated heterocycles[31]. These reactions can be explained by mechanisms similar to that illustrated for phosphorus oxychloride (scheme 4). The N-oxide group of the pyridine N-oxide (4) coordinates with the phosphorus oxychloride to give the cation (60) which then undergoes



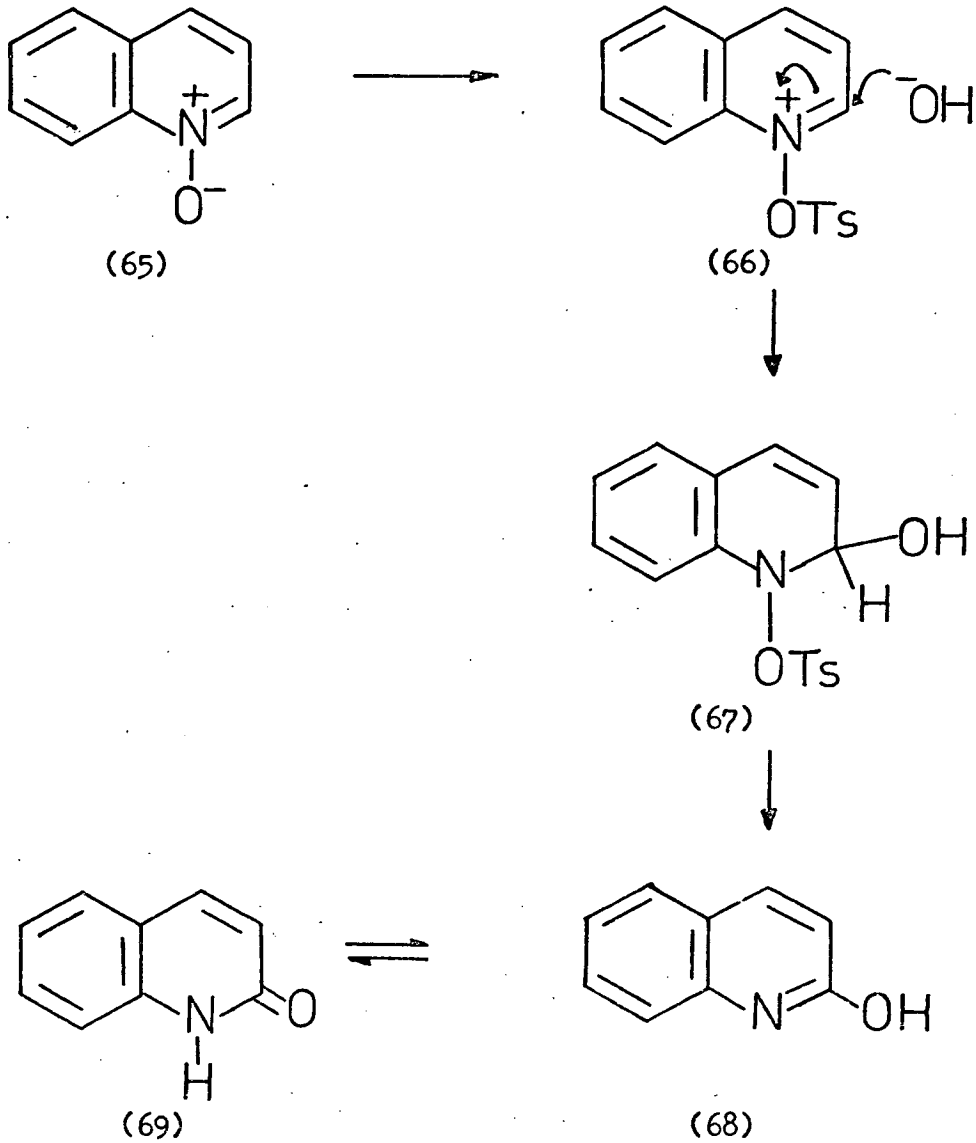
(4) (60) (61) (62)

scheme 4

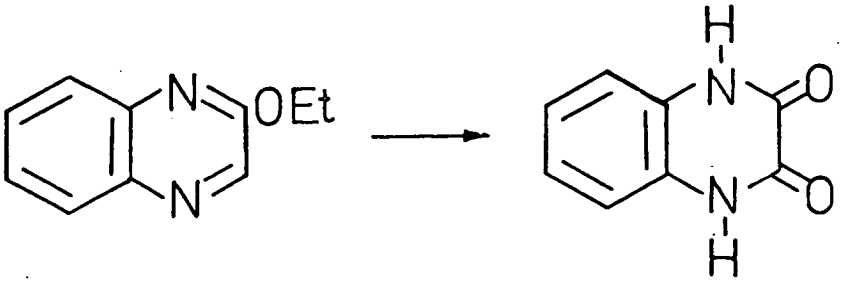
nucleophilic attack by chloride ion at the 2-position giving the intermediate (61). Expulsion of the leaving group on the nitrogen gives the 2-chlorinated heterocycle (62).

1.5 Reaction with Water or Hydroxide Ion

Some heterocyclic N-oxides readily undergo nucleophilic substitution by hydroxide ion or water to give α-oxo derivatives. Thus 3-ethoxyquinoxaline 1-oxide (63) is converted by aqueous hydrochloric acid into quinoxalin-2,3(1H,4H)-dione(64)[32].



scheme 5

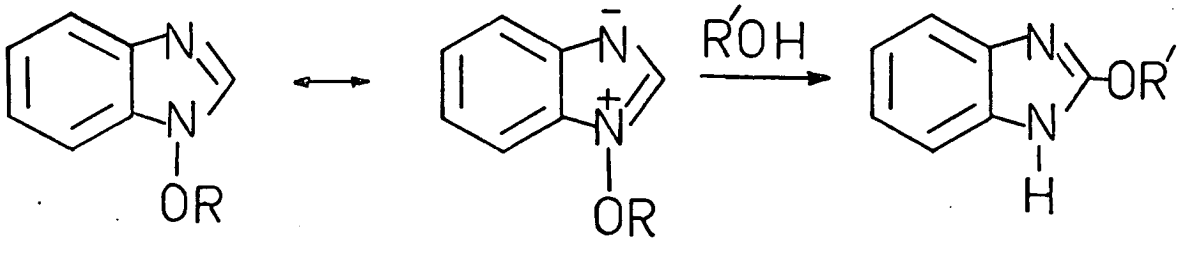


(63) (64)

Nucleophilic attack by hydroxide ion on heterocyclic N-oxides also occurs in the presence of toluene-p-sulphonyl chloride in an aqueous alkaline medium. Thus quinoline 1-oxide (65) is readily converted into 2-hydroxyquinoline (68) as shown in scheme 5[12]. The N-oxide oxygen of the quinoline 1-oxide (65) coordinates with the toluene-p-sulphonyl chloride giving the intermediate (66). Nucleophilic attack by hydroxide ion at the 2-position of the intermediate (66) gives the 2-hydroxy intermediate (67) which by elimination of the leaving group on nitrogen gives 2-hydroxyquinoline (68) which is tautomeric with the α-oxo derivative (69).

1.6 Reaction with Alcohols

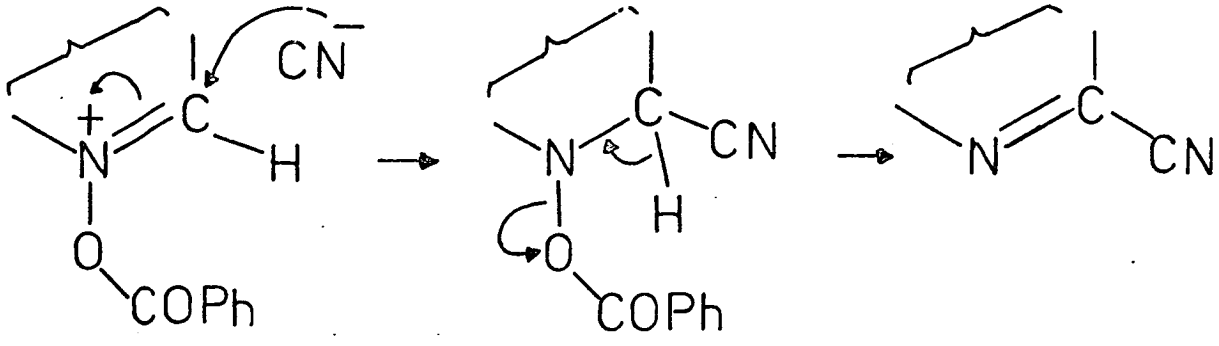
An example of nucleophilic attack by alcohols is the conversion of 1-alkoxybenzimidazoles (70) into 2-alkoxy derivatives (71) by heating under reflux in the alcohol[33].



(70) (71)

1.7 Reaction with Cyanide Ion

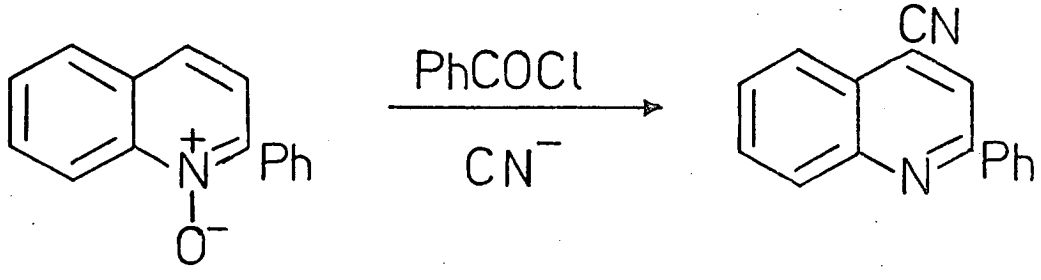
Heterocyclic N-oxides react with benzoyl chloride and aqueous potassium cyanide to give ∝-cyano derivatives (74). The course of this transformation which is analogous to the Reissert reaction is outlined in scheme 6. 2-Phenylquinoline N-oxide (75) reacts to give



(72) (73) (74)

scheme 6

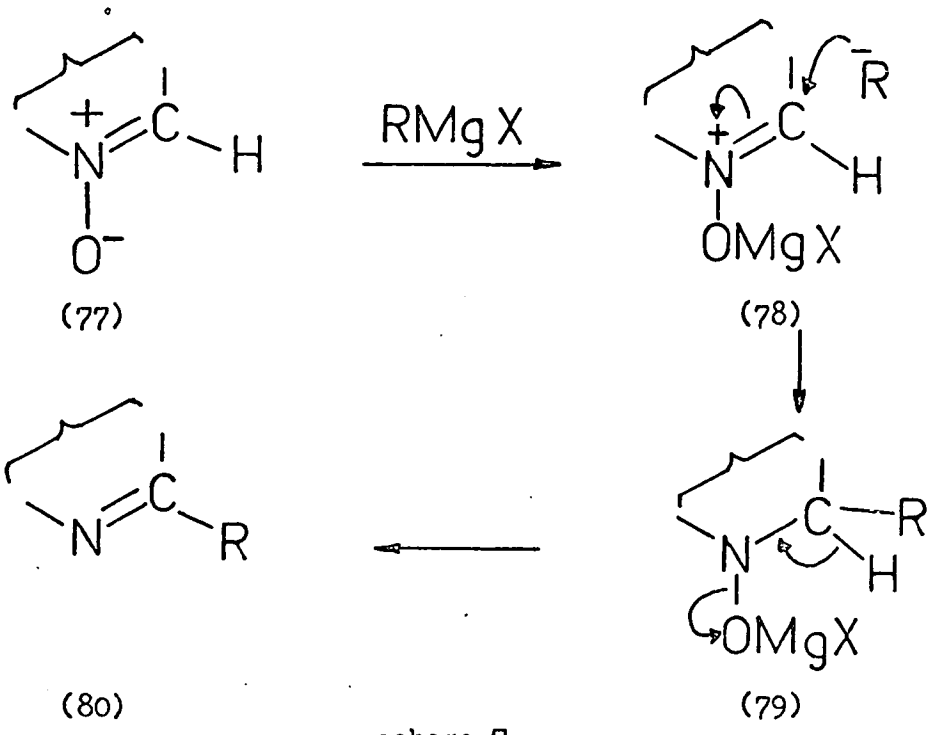
4-cyano-2-phenylquinoline (76)[34]. Pyridine N-oxide fails to react with cyanide ion in the presence of benzoyl chloride.



(75) (76)

1.8 Reaction with Organometallic Reagents

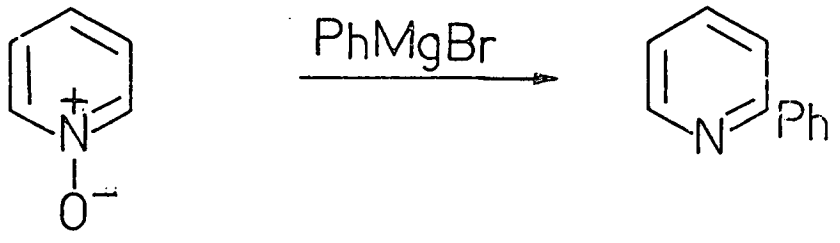
Heterocyclic N-oxides react with Grignard reagents and organolithium compounds to give ∝-alkyl and ∝-aryl heterocycles (scheme 7). The Grignard reagent coordinates with the oxygen of the N-oxide group to give the complex (78) which then undergoes



(77) (78) (80) (79)

scheme 7

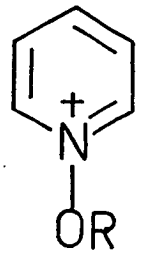
nucleophilic attack by the carbanion to yield the intermediate (79). Elimination of Mg(OH)X from the intermediate (79) gives the final product (80). This type of nucleophilic substitution is illustrated by the reaction of pyridine N-oxide with phenylmagnesium bromide to give 2-phenylpyridine (81)[35].



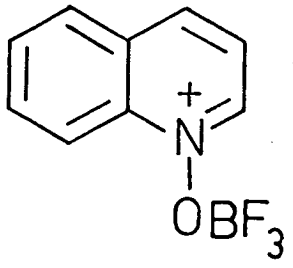
(4) (81)

1.9 Reaction with Amines

In general, amines are not sufficiently nucleophilic to attack simple heterocyclic N-oxides unless these are in the form of quaternary cations (82) or adducts with Lewis Acids (83). Amino

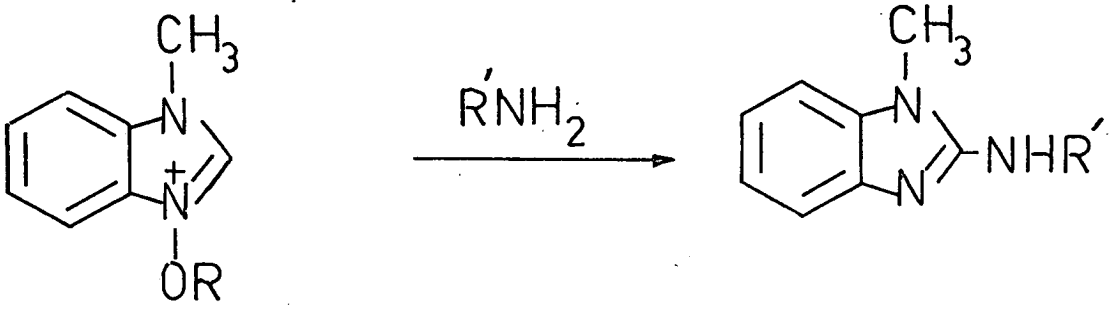


(82)



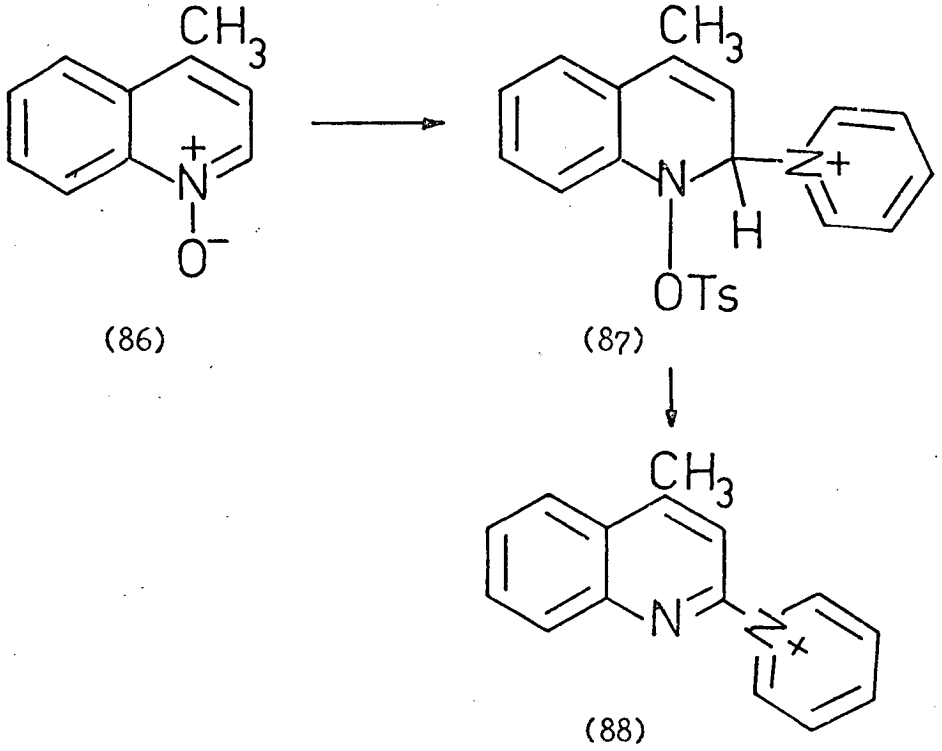
(83)

compounds react with 1-alkoxybenzimidazolium salts (84) to give products of the type (85)[36].



(84) (85)

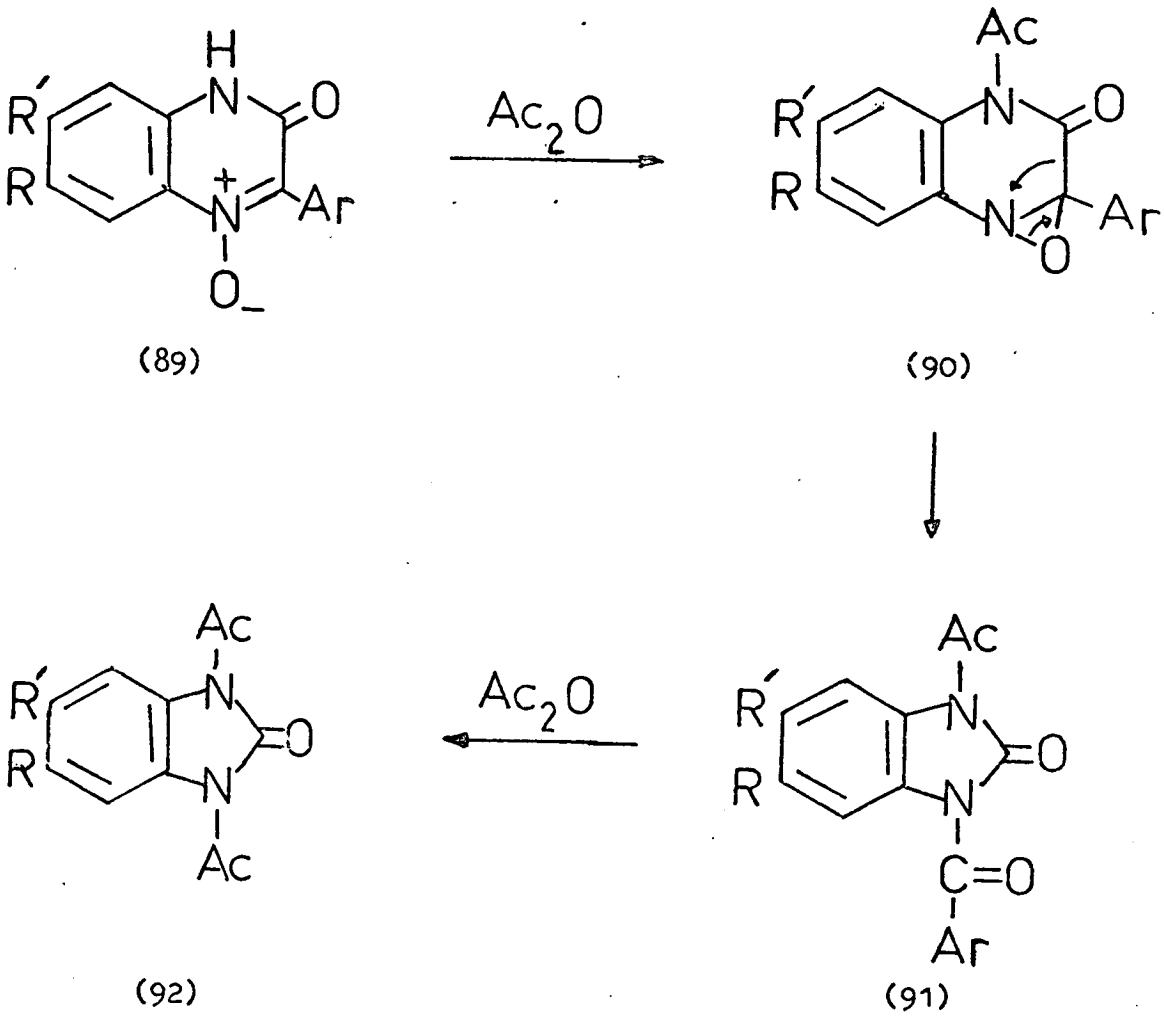
Heterocyclic N-oxides react with pyridine in the presence of toluene-p-sulphonyl chloride to give quaternary salts, substitution taking place at the α- or γ-position. Thus 4-methylquinoline 1-oxide (86) gives the cation (88) via the intermediate (87)[37].



(86) (87) (88)

Chapter Two

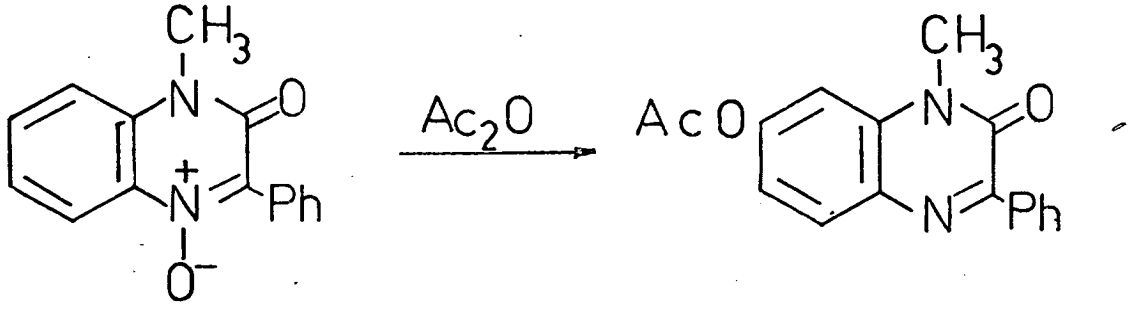
Some Studies on the Synthesis and Reactivity of Quinoxalinium Perchlorates


H
N
O
R'
R
+
N
Ar
O_
Ac2O
Ac
N
O
R'
R
N
O
Ar
(89)
(90)
Ac
N
O
R'
R
N
Ac
Ac2O
Ac
N
O
R'
R
N
C=O
Ar
(92)
(91)

scheme 8

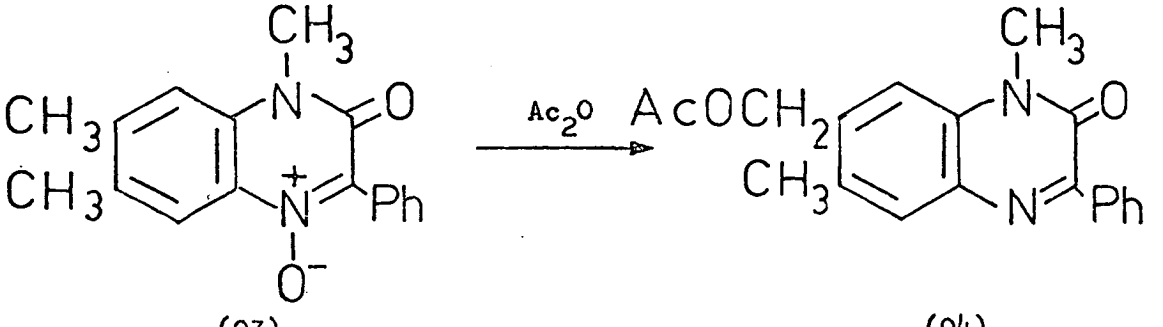
2.1 Introduction

The N-oxide (27) has been found to react with hot acetic anhydride[14,38] to produce the 7-acetoxy derivative (32). In contrast

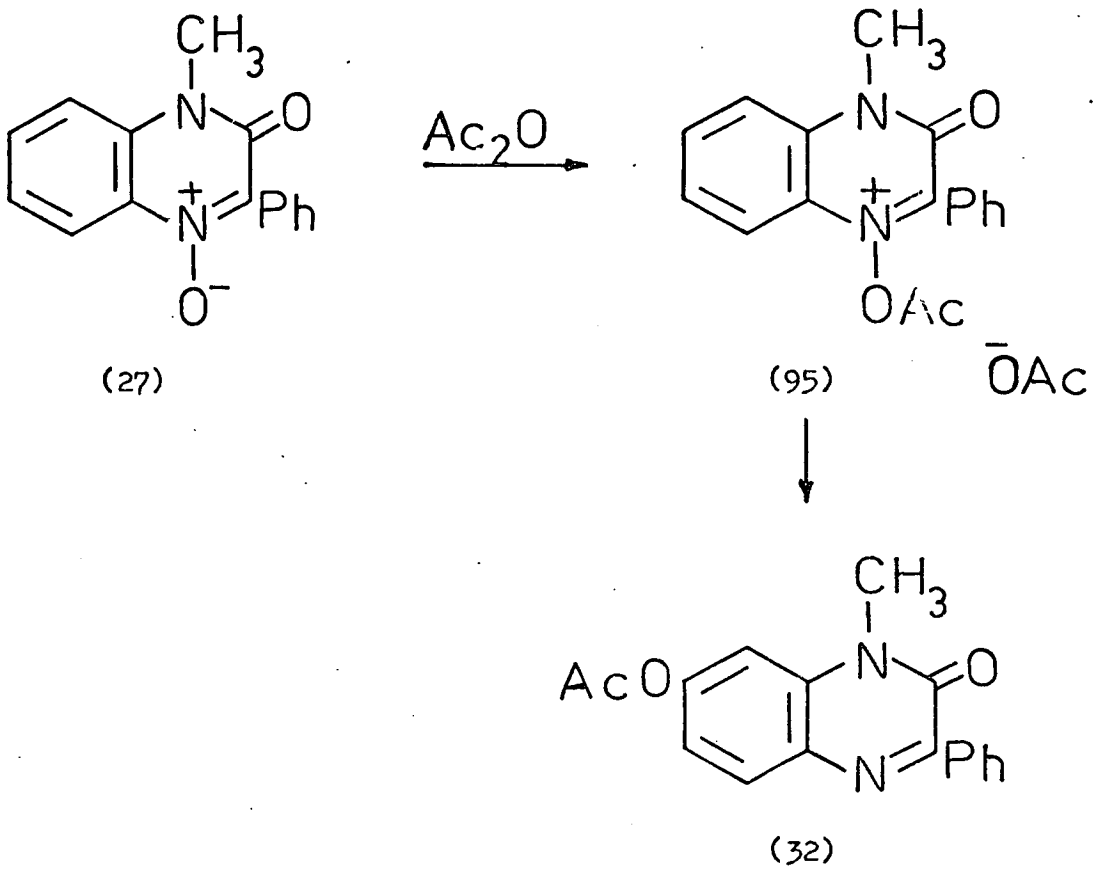


(27) (32)

3-arylquinoxalin-2(1H)-one 4-N-oxides (89) have been found to undergo ring contraction when heated with acetic anhydride to give 1-acetyl-3-acylbenzimidazolin-2-ones (91) or 1,3-diacetyl-benzimidazolin-2-ones (92)[38]. The diacetyl derivatives were formed by extending the reaction time from 3 h to 10 h. The mechanism suggested by Ahmad[38] for this ring contraction is shown in scheme 8. This ring contraction was found to be general for quinoxaline N-oxides with a substituent at C-2, a carbonyl group at C-3 and a free hydrogen at N-4. It has also been observed[39] that if a methyl group is present at the 7-position in the quinoxaline N-oxide then treatment with acetic anhydride gives a 7-acetoxymethyl derivative (93 → 94).



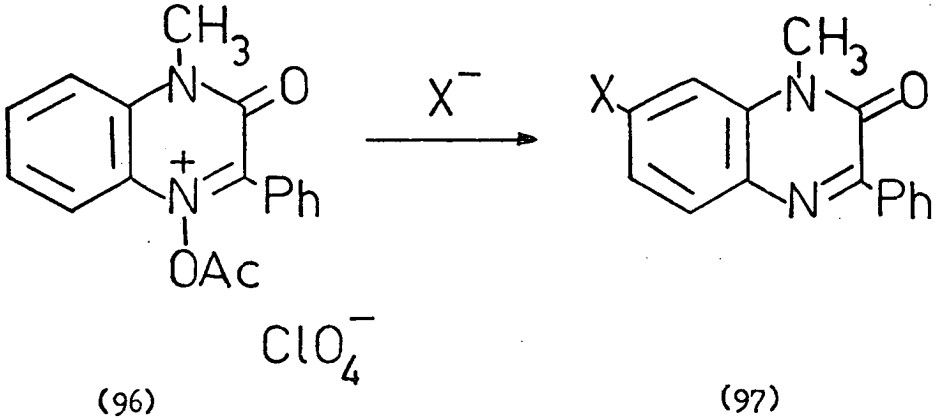
(93) (94)



(27) (95) (32)

scheme 9

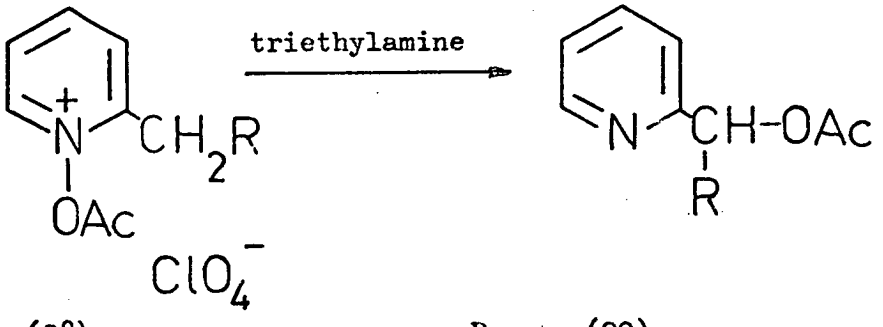
As discussed in the introduction (chapter one) the reaction of a heterocyclic N-oxide with acetic anhydride is believed to proceed by initial coordination by acetic anhydride at the N-oxide oxygen atom with the formation of a quaternary N-acetoxy acetate. Thus as shown in scheme 9, the N-oxide (27) forms the quinoxalinium acetate (95) which then reacts further to give the observed product (32).[14,38] Substitution takes place at the 7-position, which is unusual since this position is not conjugated with the N-oxide group. Nucleophilic substitution in heterocyclic N-oxides normally takes place at a position which is conjugated with the N-oxide group eg. pyridine N-oxide undergoes nucleophilic substitution at the α- and γ-positions. Since the acetoxy group is introduced into the 7-position in the product (32) it is unlikely that the rearrangement (scheme 9) goes via an <u>intramolecular</u> process, because the centre of attack is too far removed from the N-acetoxy group. If it is assumed that the rearrangement (scheme 9) is an <u>intermolecular</u> process, replacement of the acetate ion in the quinoxalinium acetate (95) by the poorly nucleophilic perchlorate ion should prevent the formation of the 7-acetoxy derivative (32). Indeed, by isolating the quinoxalinium cation as the perchlorate (96), it should be possible to introduce other nucleophiles into the molecule in place of the acetoxy group (96→97). The initial objective of the research work



(96) (97)

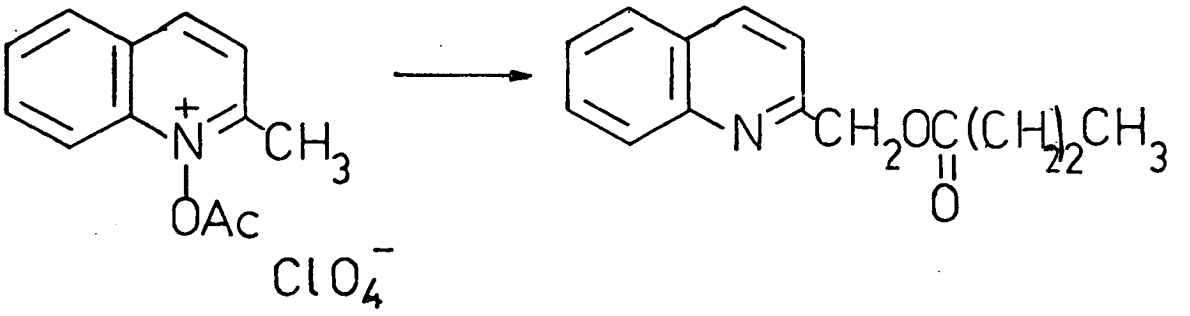
was therefore to discover whether quinoxalinium perchlorates of the type (96) were isolable and then to attempt their reaction with a variety of nucleophiles.

As mentioned in chapter one, Traynelis[9] has isolated a series of 1-acetoxy-2-alkylpyridinium perchlorates (98a) and has found that in the presence of a base such as triethylamine these perchlorates rearrange to give the acetoxy derivatives (99a). However, since the reaction of 2-alkylpyridine N-oxides with acetic



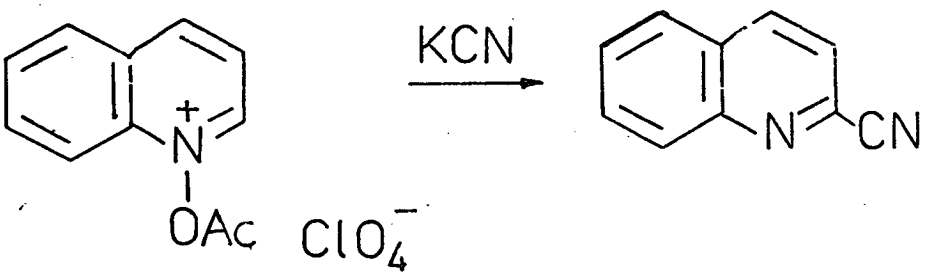
R	(98)	R	(99)
Alkyl	(a)	Alkyl	(a)
H	(b)	H	(b)

anhydride is an intramolecular process, this reaction is not strictly analogous to the reaction of the N-oxide (27) with acetic anhydride (scheme 9). Muth and Darlak[10] have prepared 1-acetoxy-2-methylpyridinium perchlorate (98b) and have shown that it reacts with sodium acetate in glacial acetic acid to give 2-acetoxymethylpyridine (99b). 1-Acetoxy-2-methylquinolinium perchlorate (100) has also been prepared and has been found to react with sodium butyrate in butyric anhydride to form 2-quinolylmethylbutyrate (101).[10]

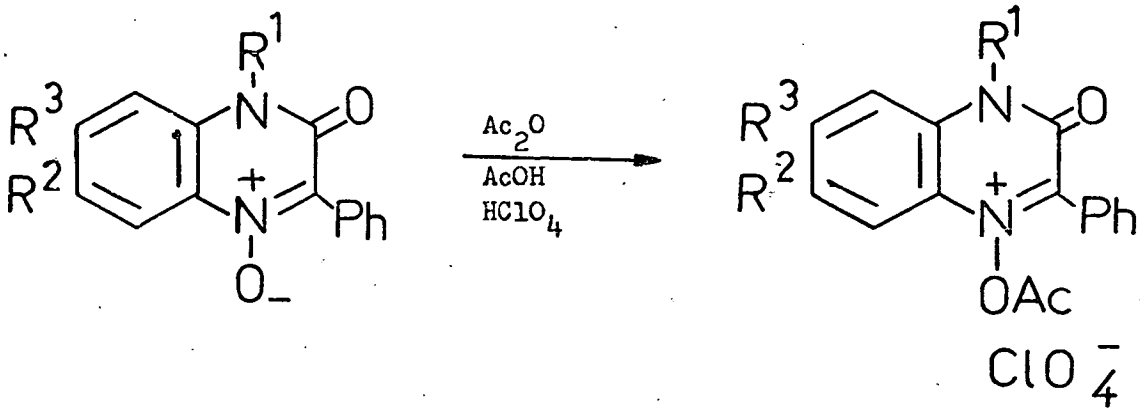


(100) (101)

1-Acetoxyquinolinium perchlorate (102) has been shown[10] to react with potassium cyanide in glacial acetic acid and acetic anhydride to give 2-cyanoquinoline (103).



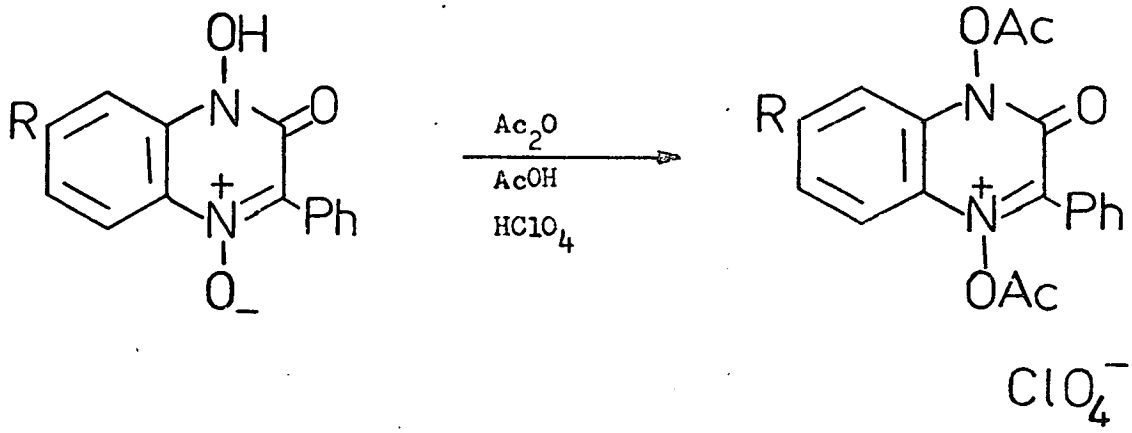
(102) (103)



(104) (105)

	R^1	R^2	R^3
(a)	CH_3	H	H
(b)	CH_3	Cl	H
(c)	CH_3	CH_3	H
(d)	CH_3	CH_3O	H
(e)	CH_3	CH_3	CH_3
(f)	H	H	H
(g)	H	Cl	H
(h)	H	CH_3	H
(i)	H	CH_3O	H
(j)	H	CH_3	CH_3

scheme 10



(106) (107)

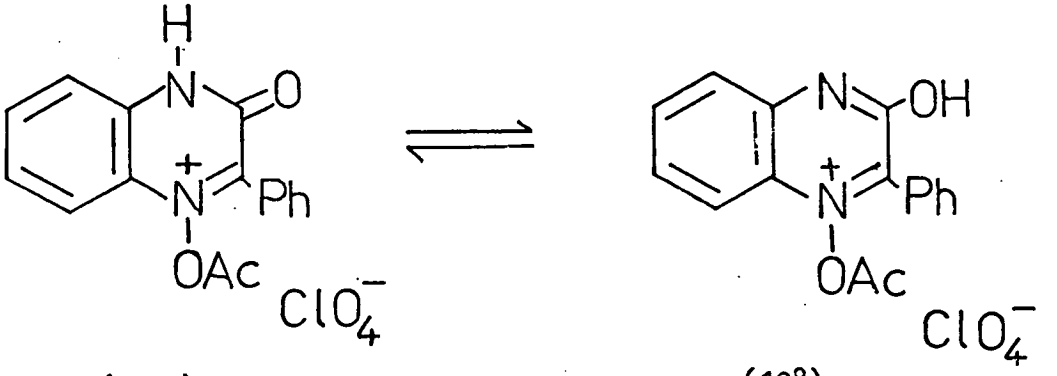
	R
(a)	H
(b)	CH_3
(c)	Cl

scheme 11

2.2 The Synthesis of 4-N-Acetoxy-1,2-dihydro-3-phenylquinoxalinium Perchlorates

The quinoxalinium perchlorates (105a-j) and (107a-c) were obtained in good yield by the reaction of the N-oxides[39-42] [(104), scheme 10 and (106), scheme 11] with acetic anhydride in the presence of perchloric acid. The quinoxalinium perchlorates were yellow to red crystalline solids which were unstable in the presence of air and light and which rapidly decomposed at room temperature to brown intractable gums. For this reason, no attempt was made to record their melting points.

The 6-methoxy perchlorate (105d) was the least stable of the 1-N-methylquinoxalinium perchlorates (105a-e) and could only be handled as a suspension in dry ether. The parent quinoxalinium perchlorate (105a) was slightly less stable than the 6-chloro compound (105b), the 6-methyl compound (105c) and the 1,6,7-trimethyl compound (105e). The perchlorates (105f-j) which did not have a substituent in the 1-position were considerably more stable than the perchlorates (105a-e), possibly because of the tautomerism which the molecules can exhibit [cf. (105f) ⇌ (108)].



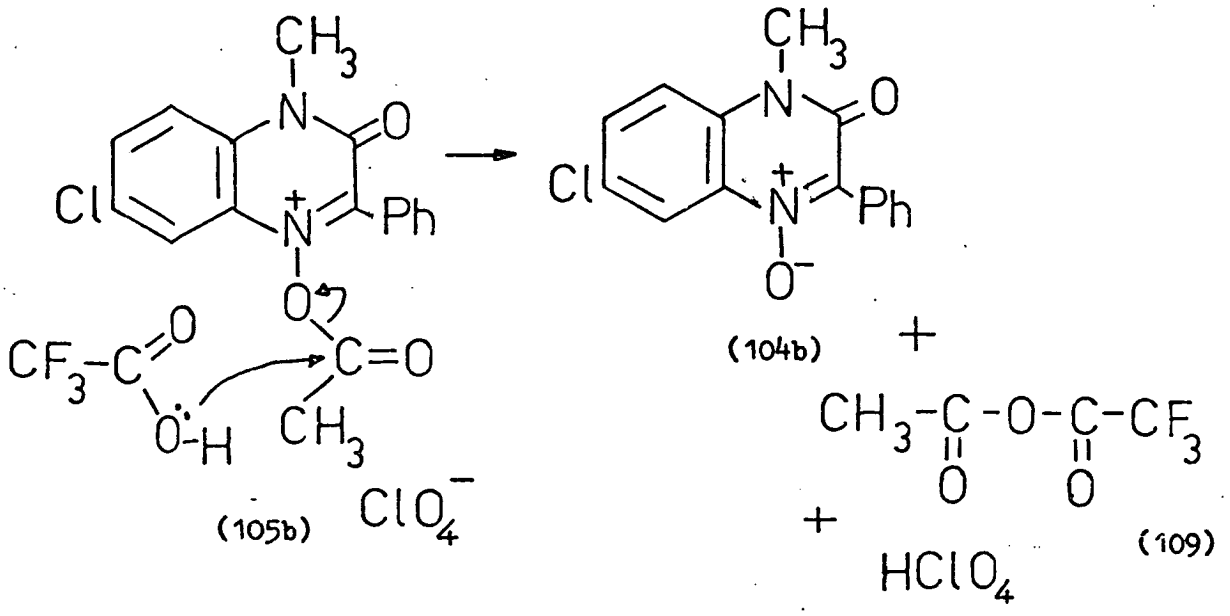
(105f) (108)

In the preparation of the perchlorates (107 a and b) from N-hydroxyquinoxaline N-oxides (106 a and b), the N-hydroxy group

was acetylated to an N-acetoxy group during the reaction. This was apparent from the presence of a carbonyl band at 1810 cm^{-1} in the i.r. spectra of these perchlorates (107 a and b) which is characteristic of a cyclic N-acetoxy group.[43]

The structures of the quinoxalinium perchlorates (105a-j) and (107 a and b) were elucidated by spectroscopy. Their i.r. spectra contained an absorption band at 1845-1830 cm^{-1} which is characteristic of a cyclic $\overset{+}{N}$.OAc group.[10] The ^1H n.m.r. spectra of the perchlorates showed a peak at τ 7.75 - 7.80 which corresponds to the grouping $\overset{+}{N}$.OAc. However, in the ^1H n.m.r. spectra of the perchlorates (105 a,c and e) this signal at τ 7.75 integrated for more than three protons. This is probably due to slight contamination of the perchlorates by acetic acid and acetic anhydride which show ^1H n.m.r. absorption at τ 7.76 and τ 7.75 respectively in trifluoroacetic acid. These perchlorates (105 a,c and e) cannot be dried thoroughly at room temperature due to their instability.

The possibility that in trifluoracetic acid the N-acetoxy group of the perchlorate (105b) was being solvolysed to the N-oxide (104b) and the anhydride (109) (scheme 12) was excluded by comparison of the ^1H n.m.r. spectrum of the perchlorate (105b) in trifluoracetic acid with that of the corresponding N-oxide (104b) in the same solvent.

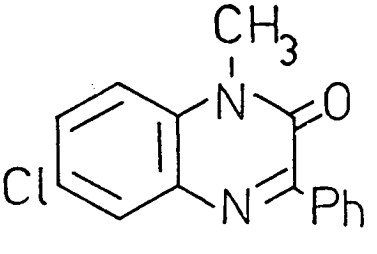


scheme 12

In the ^1H n.m.r. spectrum of the perchlorate (105b) H-5 absorbs at τ 1.57 while in the ^1H n.m.r. spectrum of the N-oxide (104b), H-5 absorbs at τ 1.42, and the two spectra are different.

The mass spectrum of the parent quinoxalinium perchlorate (105a) showed a peak at 294 mass units (M^+) which is one unit less than the molecular weight of the cation of (105a). This could be due to the formation of the 7-acetoxy derivative (32) which has a molecular weight of 294. A similar peak was also observed in the mass spectrum of the 6-methoxy perchlorate (105i) at 310 mass units (M^+), the molecular weight of the cation of (105i) being 311.

Due to the inherent instability of the quinoxalinium perchlorates and the fact that a suitable solvent could not be found from which they would crystallise unchanged, no attempt was made to have them analysed. When the perchlorates were treated with dry acetone they gave brown intractable gums. A similar result was observed with benzene, methylene dichloride and nitromethane. The perchlorates were therefore handled as suspensions in dry ether or as solutions in glacial acetic acid. The latter solvent had the disadvantage that some solvolysis of the N-acetoxy group back to the corresponding N-oxide (105 → 104) was observed (cf. scheme 12). Although some of the reaction of the perchlorates (105) were carried out in acetonitrile, it was subsequently found that in this solvent the perchlorate (105b) decomposed giving a mixture of the corresponding N-oxide (104b) and the deoxygenated compound (110b). The mechanism

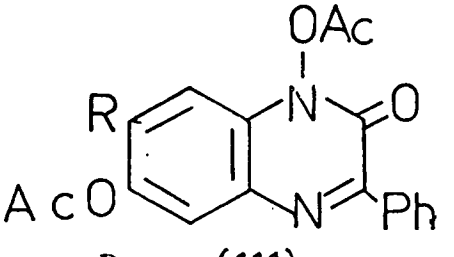


(110b)

of this reaction is not clear. It is possible however that the acetonitrile is being oxidised by the perchlorate (105b) to acetonitrile N-oxide. Pyridine N-oxide has been shown to undergo a complicated reaction with phenylacetic anhydride in which the pyridine N-oxide is reduced to pyridine with concomitant oxidation of the acid anhydride to a carbonyl compound, carbon dioxide and a carboxylic acid[4445]. However, acetic anhydride does not undergo this reaction. It is possible that a related process occurs in acetonitrile although the course involved is not clear.

The N,N-diacetoxyquinoxalinium perchlorates (107 a and b) were comparable in stability to the 1-N-methylquinoxalinium perchlorate (105a). The 7-chloro perchlorate (107c) however was very unstable and decomposed even in suspension in dry ether. The attempt to react the perchlorate (107c) with ethanol therefore gave no identifiable products.

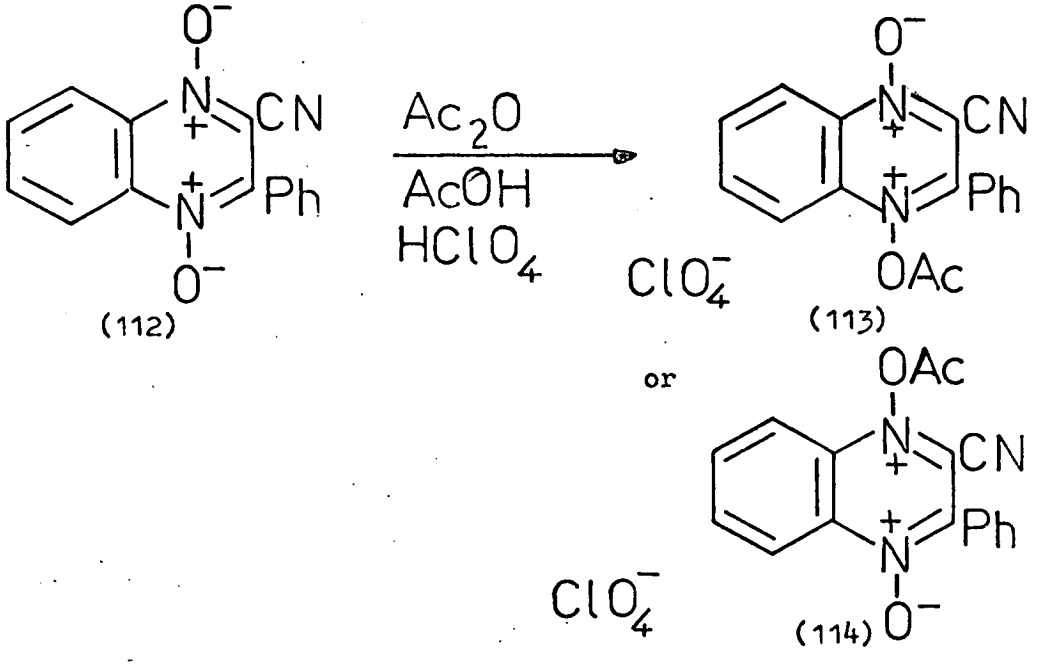
The acetic acid - acetic anhydride mother liquors from the preparation of the salts (107 b and c) gave moderate yields of compounds which are assigned the structures (111 a and b). The presence of an N-acetoxy and a C-acetoxy group was shown by the



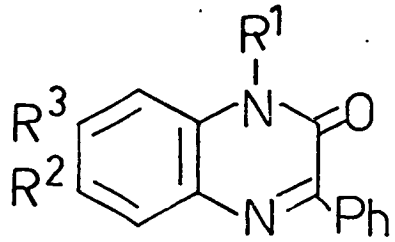
R	(111)
CH_3	(a)
Cl	(b)

characteristic absorptions at ca. 1800 and 1740 cm^{-1} respectively in the i.r. spectra of compounds (111 a and b). The ^1H n.m.r. spectra of compounds (111 a and b) contained two absorptions assignable to acetoxy groups and two singlets corresponding to H-5 and H-8. The fact that the C-acetoxy group is in the 6-position is shown by the lack of coupling in H-5 and H-8. Satisfactory mass spectral and analytical data were obtained for compounds (111 a and b).

The quinoxaline di-N-oxide (112) reacted with acetic anhydride



in the presence of perchloric acid to give a good yield of a perchlorate whose structure is formulated as (113) or (114). The presence of the $\overset{+}{N}\cdot OAc$ group was shown by the characteristic absorption at 1820 cm^{-1} in the i.r. spectrum. The ^1H n.m.r. spectrum of the compound indicated the presence of one acetoxy group. On the spectroscopic data available, it is impossible to distinguish between structures (113) and (114). On attempted crystallisation from ethanol, the perchlorate (113) or (114) was converted to the di-N-oxide (112) and analytical data for the perchlorate could not therefore be obtained.



(115)

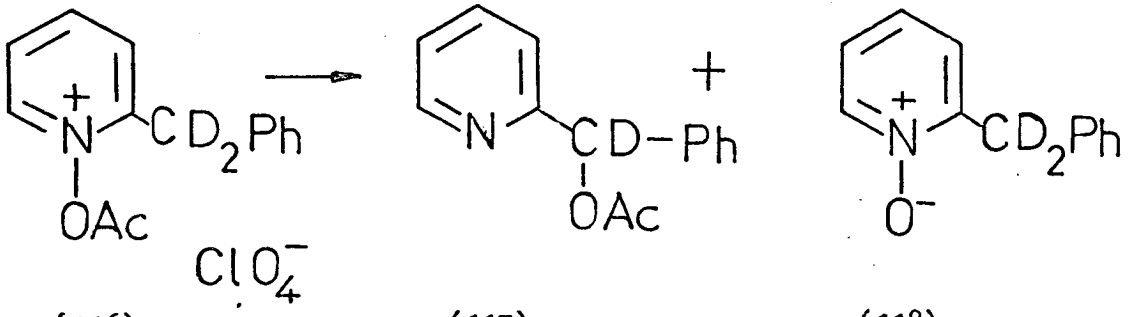
	R^1	R^2	R^3
(a)	CH_3	H	OAc
(b)	CH_3	Cl	OAc
(c)	CH_3	CH_3	CH_2OAc
(d)	CH_3	CH_3	CH_2OH
(e)	H	H	OAc
(f)	CH_3	Cl	N_3
(g)	CH_3	Cl	OH
(h)	CH_3	H	OH
(i)	CH_3	Cl	SCN
(j)	CH_3	Cl	Cl
(k)	CH_3	CH_3	Cl

2.3 The Reactions of Quinoxalinium Perchlorates with Anions

(a) Sodium Acetate

As discussed earlier, the N-oxide (104a) reacts with hot acetic anhydride to give the 7-acetoxy derivative (115a).[14,38] Since the N-acetoxyquinoxalinium acetate (95) has been suggested as the probable intermediate[14] in this reaction, once this intermediate had been isolated as the perchlorate (105a), it was of interest to study its reaction with sodium acetate in ether and also in glacial acetic acid. These reactions gave a good yield of the 7-acetoxy derivative (115a) which was characterised by comparison with an authentic sample. Thus the fact that the perchlorate (105a) reacts with sodium acetate to give the same product (115a) as that obtained in the reaction of the N-oxide (104a) with hot acetic anhydride supports the probability that the intermediate in this reaction is the N-acetoxyquinoxalinium acetate (95). The perchlorate (105b) likewise reacted with sodium acetate in ether and in glacial acetic acid to give high yields of the 7-acetoxy derivative (115b).

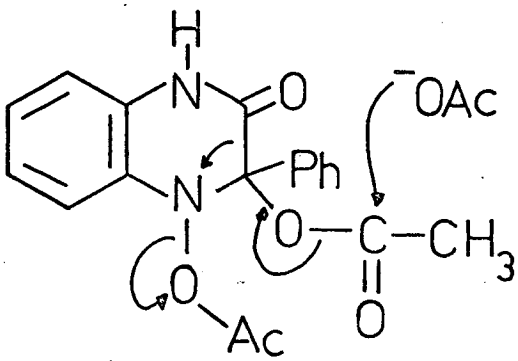
Traynelis[9] has reported a reaction similar to those described above. He has prepared the deuterated 2-alkyl pyridinium perchlorate (116) and has found that this reacts with sodium acetate in the presence of acetic acid and acetonitrile to give the rearranged ester (117) and the N-oxide (118). The fact that the N-oxides



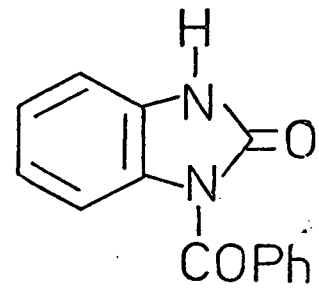
(104 a and b) were not obtained in the reactions of the quinoxalinium perchlorates (105 a and b) with sodium acetate in glacial acetic acid indicates that nucleophilic attack by acetate ion must take place much faster than solvolysis of the N-acetoxy group back to the N-oxide. The ease with which these reactions occur is also demonstrated by the fact that the sodium acetate reacts with the quinoxalinium perchlorate even in suspension in ether in which the concentration of acetate ion would be expected to be very small.

As an extension of these studies, the reaction of a 7-substituted perchlorate with sodium acetate in glacial acetic acid was carried out. For synthetic reasons, the perchlorate (105e) was used. This reaction was of interest because with the 7-position blocked, the reaction could either take place at the substituent or at some other position in the molecule. The product from the reaction contained a carbonyl band at 1730 cm^{-1} which is characteristic of a C-acetoxy group. However, when the product was purified by column chromatography on alumina, the 7-hydroxymethyl derivative (115d) was obtained in good yield and was characterised by comparison with an authentic sample.[14] It seems probable that the initial product from the reaction is the 7-acetoxymethyl compound (115c) which then undergoes hydrolysis on the alumina column to the 7-hydroxymethyl compound (115d). Thus the reaction of sodium acetate with the perchlorate (105e) gives the same product as is obtained on treatment of the N-oxide (104e) with hot acetic anhydride.[14,39]

In view of the ring contraction observed[38] when 3-arylquinoxalin-2(1H)-one 4-N-oxides (89) are heated with acetic anhydride, it was of interest to prepare the perchlorate (105f) in order to see whether this perchlorate would react with sodium acetate

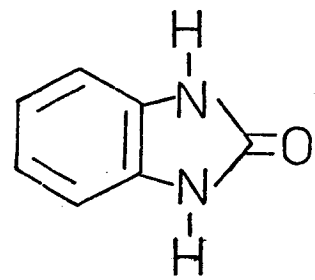


(120)



(121)

EtOH Solvolysis



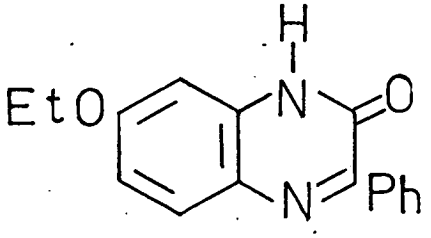
(122)

+

$PhCO_2Et$

scheme 13

to give a 7-acetoxy derivative (115e) or whether it would give a ring contracted product. The reaction was initially carried out in dry ether. After the addition of ethanol to destroy any unreacted perchlorate, the product obtained was washed with light petroleum and then chromatographed on silica. The only product identified from the column was 7-ethoxy-3-phenylquinoxalin-2(1H)-one (119). The other product obtained was a mixture of the 7-ethoxy compound



(119)

(119) and another compound which contained only aromatic protons. This was established by comparison of the ^{1}H n.m.r. spectrum of the mixture with the ^{1}H n.m.r. spectrum of a pure sample of the 7-ethoxy compound (119). However, ethyl benzoate was also isolated suggesting that some ring contraction had taken place. Formation of ethyl benzoate as a by-product is explained by the reaction mechanism outlined in scheme 13. The perchlorate (105f) undergoes nucleophilic attack by acetate ion at the 2-position giving the intermediate (120). Ring contraction of (120) as shown then gives the benzimidazolin-2-one (121) which undergoes solvolysis by ethanol to give the benzimidazolin-2-one (122) and ethyl benzoate (scheme 13).

In contrast to the reaction in dry ether, reaction of the

perchlorate (105f) with sodium acetate in glacial acetic acid, resulted in some solvolysis of the N-acetoxy group back to the N-oxide (104f). A solid was also obtained which contained an absorption band at 1755 cm^{-1} in its i.r. spectrum and a peak in its ^1H n.m.r. spectrum at τ 7.51. These spectroscopic properties are characteristic of a C-acetoxy group. The integration of the ^1H n.m.r. spectrum however indicated that the product was not homogeneous, because the integral due to the aromatic proton resonances was much larger than it should be if the solid were a single compound containing an acetoxy group. The mass spectrum of the solid contained a peak at 280 mass units corresponding to the molecular weight of the 7-acetoxy derivative (115e) and a peak at 238 mass units corresponding to the N-oxide (104f). The t.l.c. of the mixture is organic solvents over silica and alumina indicated a single component and since both components are acidic, their separation by column chromatography was not attempted. Attempts to separate the mixture by crystallisation were unsuccessful and thus a pure sample of the 7-acetoxy compound (115e) was not obtained.

The perchlorate (105j) reacted with sodium acetate in ether to give a low yield of the N-oxide (104j) which was characterised by comparison with an authentic sample. No product containing an acetoxy group was isolated from the reaction mixture.

The scope of the reactions of the quinoxalinium perchlorates [(105)and (107)] with other anions was also investigated.

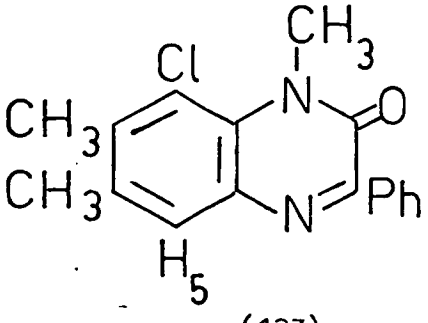
(b) Lithium Chloride

The perchlorate (105b) was found to react with lithium chloride in dry ether to give a moderate yield of the 6,7-dichloro compound (115j) and a low yield of the 7-hydroxy compound (115g). These

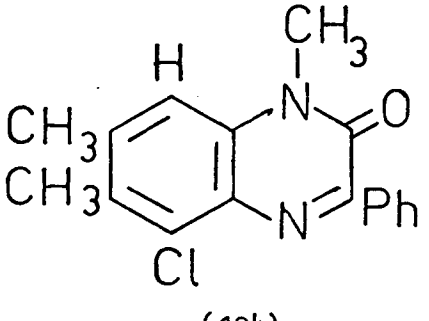
products, which were characterised by comparison with authentic samples,[14] must be derived by nucleophilic attack on the perchlorate (105b) by chloride ion and hydroxide ion or water respectively.

The perchlorates (105 b and c) also reacted with lithium chloride in glacial acetic acid to give moderate yields of the 7-chloro derivatives (115 j and k) respectively. Solvolysis of the perchlorates (105 b and c) also occurred giving good yields of the corresponding N-oxides (104 b and c) (cf. scheme 12). The 7-chloro derivatives (115 j and k) were characterised by comparison with authentic samples.

The effect of having a substituent in the 7-position was again investigated by reacting the perchlorate (105e) with lithium chloride in glacial acetic acid. The main product obtained in good yield from this reaction was the N-oxide (104e). Two monochloroquinoxalinone derivatives were also isolated in low yield. The ^{1}H n.m.r. spectra of these monochloro compounds lacked benzyl absorption indicating that no attack on the 6- or 7-methyl groups had taken place. The ^{1}H n.m.r. spectra of the monochloro compounds contained single aromatic proton resonances at τ 2·42 and τ 3·10 respectively. These compounds are therefore designated as the 8-chloro (123) and 5-chloro (124) compounds respectively, because in the ^{1}H n.m.r.



(123)

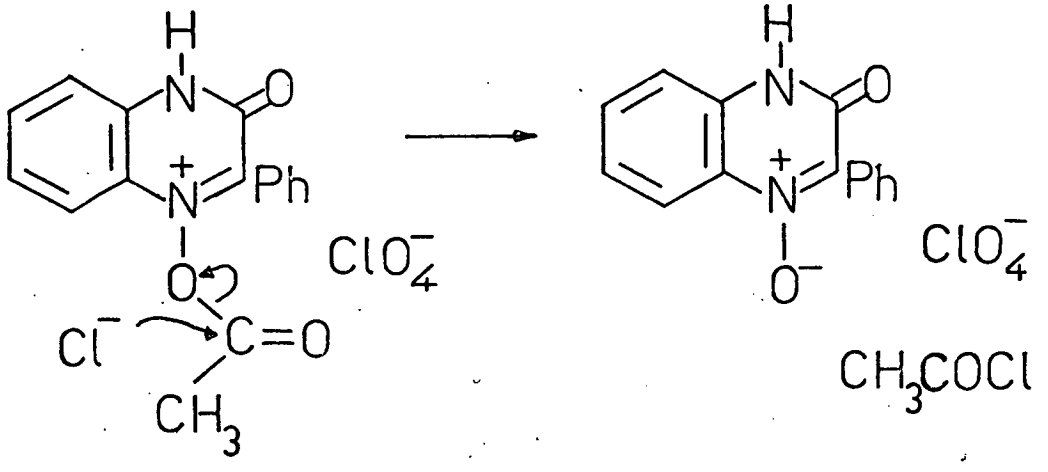


(124)

spectra of the quinoxalinones studied in this work, the proton at the 5-position absorbs at lower field than the proton at the 8-position.

It should be noted that compound (123) now assigned the 8-chloro structure was obtained previously by treatment of the N-oxide (104e) with acetyl chloride and incorrectly assigned the 5-chloro structure.[14]

The reaction of the unsubstituted perchlorate (105f) with lithium chloride in glacial acetic acid gave a high yield of the corresponding N-oxide (104f). The N-oxide (104f) could be formed by solvolysis of the perchlorate (105f) by acetic acid (cf. scheme 12) or by nucleophilic attack by chloride ion at the N-acetoxy group (scheme 14). Nucleophilic attack at the carbonyl group of an

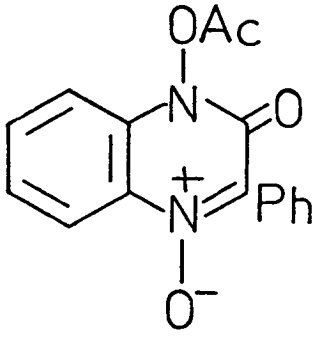


(105f) (104f)

scheme 14

N-acetoxy quaternary salt to give the corresponding N-oxide has been reported as a characteristic reaction of such compounds by Muth and Darlak[10] and also by Traynelis.[9]

The 1,4-diacetoxy perchlorate (107a) also reacted with lithium chloride in glacial acetic acid to give a good yield of the 1-N-acetoxy N-oxide (125), which was characterised by comparison



(125)

with an authentic sample.[14] No product corresponding to attack on the perchlorate (107a) by chloride ion was isolated in this experiment.

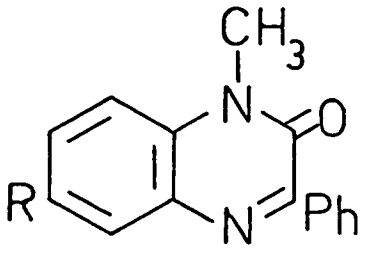
(c) Lithium Bromide

The perchlorate (105b) reacted with lithium bromide in glacial acetic acid and also in dry ether to give high yields of the N-oxide (104b). These reactions probably involve attack by bromide ion at the N-acetoxy group in the perchlorate (105b) (cf. scheme 14) since the perchlorate is stable in dry ether and does not spontaneously decompose to the N-oxide (104b). The reaction was worked up by the addition of water and only a small amount of the 7-hydroxy compound (115g) was obtained. This demonstrates that the perchlorate (105b) had largely been converted into the N-oxide (104b) in the reaction mixture before the addition of the water since the perchlorate (105b) reacts with water to give the 7-hydroxy compound (115g) and not the N-oxide (104b).

(d) Sodium Thiocyanate

Sodium thiocyanate reacted with the 6-chloroquinoxalinium perchlorate (105b) in glacial acetic acid to give moderate yields of the 7-thiocyanato compound (115i), and the N-oxide (104b) and a low

yield of the deoxygenated compound (110b). The structure of (110b)



R	(110)
H	(a)
Cl	(b)

was confirmed by comparison with an authentic sample.[14] The 7-thiocyanato compound (115i) was also obtained in lower yield by carrying out the reaction in dry ether. The i.r. spectrum of (115i) contained a band at 2200 cm^{-1} which is characteristic of a thiocyanato group. In the ^1H n.m.r. spectrum of (115i) there were two singlets corresponding to two aromatic protons. The absence of any splitting in these singlets uniquely defines the position of substitution in the molecule as C-7 since substitution at any other site would lead to observable splitting in the aromatic protons. The mass spectrum and the analysis of (115i) were also in accord with the assigned structure.

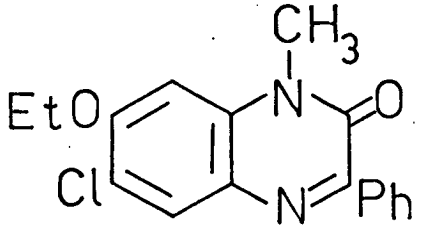
(e) Sodium Amide

The perchlorate (105b) reacted with sodium amide in ether to give a low yield of the deoxygenated compound (110b). As mentioned previously, the formation of this product in these nucleophilic substitution reactions is difficult to rationalise.

(f) Metal Cyanides

As mentioned earlier, 1-acetoxyquinolinium perchlorate (102) has been found to react with potassium cyanide in acetic acid and acetic anhydride to give a low yield of 2-cyanoquinoline (103).

In the present studies, attempts to introduce a cyano group into the quinoxaline nucleus by reaction of the quinoxalinium perchlorates (105 a and b) with metal cyanides were unsuccessful. The parent quinoxalinium perchlorate (105a) reacted with aqueous potassium cyanide and with sodium cyanide in dimethylformamide to give high yields of the 7-hydroxy compound (115h) the structure of which was confirmed by comparison with an authentic sample.[14] In the latter reaction the 7-hydroxy compound (115h) was probably formed on work up since water was added. Similarly, the perchlorate (105b) reacted with sodium cyanide in ether to give a high yield of the 7-hydroxy-6-chloro compound (115g) which was characterised by its ^{1}H n.m.r., i.r. and mass spectra and its elemental analysis. When this reaction was repeated using silver cyanide and the reaction mixture was worked up with ethanol, a good yield of the 7-ethoxy compound (126c)



(126c)

was obtained indicating that there was a large amount of unreacted quinoxalinium perchlorate (105b) present. A low yield of the 7-hydroxy compound (115g) was also obtained.

It would appear from these results that cyanide ion is a poor nucleophile in reactions of the N-acetoxyquinoxalinium perchlorates (105 a and b). Any hydroxide ion present in the reaction mixture

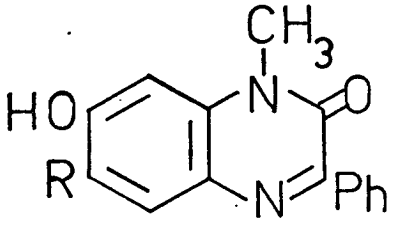
reacts with the N-acetoxyquinoxalinium perchlorate before the cyanide ion has a chance to compete.

(g) Sodium Azide

The reaction of the perchlorate (105b) with sodium azide in dry ether produced a low yield of a compound whose spectroscopic properties were consistent with the 7-azido-6-chloro structure (115f). The i.r. spectrum contained an absorption band at 2175 cm^{-1} assignable to the azido-group and the ^{1}H n.m.r. spectrum showed two uncoupled single aromatic protons indicating the presence of a substituent in the 7-position. The compound however was obtained in low yield and deteriorated on standing. Consequently there was insufficient material to fully characterise the compound (115f) by elemental analysis.

2.4 The Reactions of Quinoxalinium Perchlorates with Alkali and Water

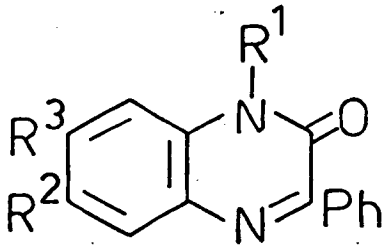
The perchlorate (105a) was found to react with 5M aqueous sodium hydroxide to give a good yield of the 7-hydroxy derivative (115h). This reaction can be considered as being analogous to the reactions of the perchlorates (105) with anions with the hydroxide ion being the nucleophilic species in this case. The facility



R	(115)
Cl	(g)
H	(h)

of the formation of the 7-hydroxy derivatives is demonstrated by the fact that the perchlorate (105b) reacted with water to give a high yield of the 7-hydroxy compound (115g) which was characterised by comparison with a sample obtained before.

Attempts to react the perchlorates (105f) and (107a) with water gave brown solids which could not be purified by crystallisation. Purification of the solids by column chromatography was not attempted since in the case of the perchlorate (105f) the starting material is acidic and in the case of the perchlorate (107a) the starting material contains an N-acetoxy group which would be hydrolysed on the column to an acidic N-hydroxyl group. These acidic products would not elute from the column.



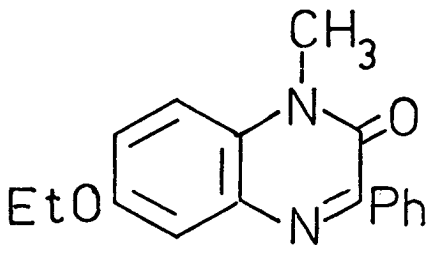
(126)

	R^1	R^2	R^3
(a)	CH_3	H	OEt
(b)	CH_3	H	OCH_3
(c)	CH_3	Cl	OEt
(d)	CH_3	Cl	OCH_3
(e)	CH_3	Cl	$OCH(CH_3)_2$
(f)	CH_3	CH_3	OEt
(g)	CH_3	CH_3	OCH_3
(h)	CH_3	OCH_3	OEt
(i)	CH_3	OCH_3	OCH_3
(j)	CH_3	CH_3	CH_2OEt
(k)	CH_3	CH_3	CH_2OCH_3
(l)	H	H	OEt
(m)	H	H	OCH_3
(n)	H	Cl	OEt
(o)	H	Cl	OCH_3
(p)	H	CH_3	OEt
(q)	H	CH_3	OCH_3
(r)	H	OCH_3	OEt
(s)	H	OCH_3	OCH_3
(t)	H	CH_3	CH_2OEt

2.5 The Reactions of Quinoxalinium Perchlorates with Alcohols

The quinoxalinium perchlorates (105a-d) were found to react with ethanol and methanol to give good yields of the 7-ethoxy (126 a,c,f and h) and 7-methoxy compounds (126 b,d,g and i) respectively. The yield of the 7-methoxy compound (126b) was lower than the yields of the other ethers (126 a,g and i) due to the fact that this reaction was worked up by extraction with chloroform and trituration with organic solvents. In the compound (126a), the presence of the ethoxyl group was demonstrated by the fact that the ^{1}H n.m.r. spectrum contained a quartet at τ 5.88 and a triplet at τ 8.54. The fact that the substituent had entered the 7-position in the quinoxaline nucleus was indicated by the splitting pattern in the ^{1}H n.m.r. spectrum which was characteristic of a 1,2,4-trisubstituted benzene derivative. The signal at τ2.21 is assigned to H-5 because this proton showed up as a doublet with a coupling constant of 9.0 Hz which is characteristic of the coupling constant between aromatic protons ortho to one another on a benzene ring. The signal farther upfield at τ 3.13 is assigned to H-6 because it appears as a double doublet with coupling constants corresponding to ortho and meta coupling between aromatic protons. The signal at highest field (τ3.34) is assigned to H-8 because the ^{1}H n.m.r. signal is a doublet with a coupling constant corresponding to meta coupling between aromatic protons. The i.r. and mass spectra, and the analytical data for the compound were also fully in accord with the 7-ethoxy structure (126a). It should be noted that the evidence for the structure of compound (126a) so far cited does not exclude the possibility that substitution could have taken place in the 6-position to give the

6-ethoxy compound (127). However, it has already been shown that in



(127)

the reactions with anions and water, nucleophilic attack on the perchlorates (105) takes place at the 7-position. Also, in the reaction of the N-oxide (104a) with acetic anhydride,[14,38] the acetoxy group is introduced into the 7-position. It seems likely therefore that in the reaction of the perchlorate (105a) with ethanol, nucleophilic attack has taken place at the 7-position leading to the 7-ethoxy compound (126a). Further evidence in support of the 7-ethoxy structure (126a) was obtained in the reaction of the perchlorate (105a) with methanol to give the 7-methoxy derivative (126b), the structure of which has been proved unequivocally by Ahmad.[38]

The quinoxalinium perchlorates (105 b,c and d) which have a substituent in the 6-position reacted with ethanol and methanol to give products (126 c,d and f-i) in which the position of substitution was unambiguously shown to be at C-7 by the lack of aromatic coupling in the H-5 and H-8 protons in the ^{1}H n.m.r. spectra. Satisfactory i.r. spectra and analytical data were obtained for all of these products.

The secondary alcohol isopropanol was shown to react in a similar way with the perchlorate (105b) giving a good yield of the

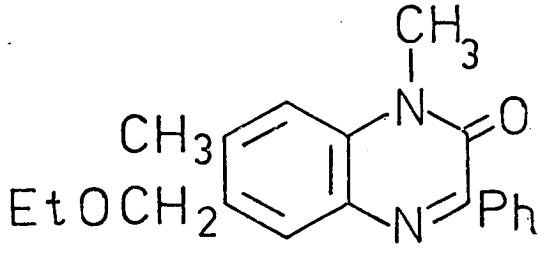
7-isopropoxy compound (126e). The presence of the isopropoxy group was shown by the ^{1}H n.m.r. spectrum and the i.r. spectrum and analytical data were consistent with the 7-isopropoxy structure (126e).

The ease with which the perchlorates (105 a-d) react with alcohols was demonstrated by the fact that the presence of the strongly electron-donating methoxyl group in the perchlorate (105d) does not inhibit its reaction with ethanol or methanol.

Since ring contraction is observed[38] when 3-arylquinoxalin-2(1H)-one 4-N-oxides (89) are heated with acetic anhydride, it was of interest to study the reaction of N-unsubstituted quinoxalinium perchlorates (105 f-i) with alcohols. It was found that the perchlorates (105 f-i) reacted with ethanol and methanol to give good yields of the 7-ethoxy (126 l,n,p and r) and 7-methoxy (126 m,o,q and s) quinoxalinones respectively. The position of substitution in the 7-ethoxy compound (126l) was again shown by the splitting pattern in the ^{1}H n.m.r. spectrum, which was characteristic of a 1,2,4-trisubstituted benzene derivative. The possibility that substitution had taken place at the 6-position is excluded by the fact that the proton at highest field, H-8, is meta coupled indicating that the substituent is in the 7-position. The spectral and analytical data obtained for compounds (126 l-s) were fully in accord with their assigned structures. No products derived from a ring contraction process were isolated in the reactions of the salts (105 f-i) with alcohols.

Since it was found that alcohols reacted with the perchlorates (105 a-d and f-i) at the 7-position, it was of interest to study the reactions of alcohols with a quinoxalinium perchlorate in which

the 7-position was blocked by a substituent. The perchlorate (105e) was found to react with ethanol and methanol to give good yields of products whose spectral and analytical data were consistent with their being the 7-ethoxymethyl compound (126j) and the 7-methoxymethyl compound (126k) respectively. This was shown by the ^{1}H n.m.r. spectrum of the compound (126j) which contained two singlets in the aromatic region corresponding to H-5 and H-8, a singlet at τ 5.43 corresponding to a methylene group, two singlets at τ 6.28 and τ 7.65 corresponding to an N-methyl and a C-methyl group respectively, and an ethoxyl group at τ 6.35 (quartet) and τ 8.70 (triplet). The i.r. spectrum and the analytical data were also consistent with the 7-ethoxymethyl structure (126j). The structure of the 7-methoxy derivative (126k) was deduced in the same way. It should be noted that the evidence for the structure of compound (126j) does not exclude the possibility that attack could have taken place at the 6-methyl group giving the 6-ethoxymethyl derivative (128) which is isomeric with compound (126j) and would



(128)

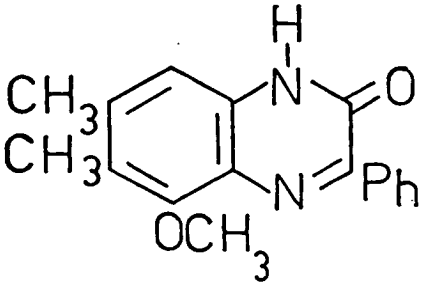
have similar spectral properties. The product from the reaction of the perchlorate (105e) with ethanol is assigned the 7-ethoxymethyl structure (126j) on the basis that it has been shown previously [39] that the N-oxide (104e) undergoes nucleophilic attack at the

7-methyl group when reacted with acetic anhydride to give the 7-acetoxymethyl derivative (115c). Also, when the 1,6-dimethylquinoxalinium perchlorate (105c) reacted with ethanol, attack could be shown unequivocally to have taken place at the 7-position by the presence of two uncoupled aromatic protons in the ^{1}H n.m.r. spectrum of the product (126f). There was no evidence to suggest that attack had taken place at the 6-methyl group in the perchlorate (105c). In the reactions of the perchlorate (105e) with ethanol and methanol, no products were isolated which corresponded to attack at the 5- or 8-positions in the molecule.

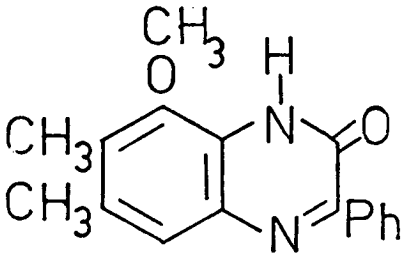
When the perchlorate (105j) was reacted with ethanol, a product was obtained in moderate yield which was shown to be the 7-ethoxymethyl derivative (126t) by the fact that its ^{1}H n.m.r. spectrum contained two methylene absorptions, one a singlet and one a quartet. Satisfactory i.r. and mass spectral and analytical data were obtained for the product. Attack was considered to have taken place at the 7-methyl group by analogy with the previous results obtained for the reaction of the perchlorate (105e) with ethanol and methanol.

The perchlorate (105j) reacted with methanol however, to give a moderate yield of a product whose ^{1}H n.m.r. spectrum showed an absorption at τ 7.48 which was attributable to two C-methyl groups. The ^{1}H n.m.r. spectrum also contained a methoxyl group at τ 5.90 and a multiplet in the aromatic region corresponding to six aromatic protons demonstrating that the product was the 5-methoxy derivative (129). The i.r. and mass spectral data and the analysis of the product were also fully in accord with structure (129). On the

evidence cited however, attack at the 8-position to give the



(129)



(130)

8-methoxy derivative (130) cannot be excluded. The product is assigned the 5-methoxy structure because it has been shown previously that quinoxaline N-oxides which have a substituent in the 7-position can undergo nucleophilic attack at the 5-position.[14]

The 1-N-acetoxyquinoxalinium perchlorate (107a) reacted with ethanol to give a moderate yield of a product whose spectral properties were consistent with its being the 1-N-acetoxy-7-ethoxy-quinoxalinone (131a). The ^{1}H n.m.r. spectrum of the product showed signals at τ5.89 (quartet) and τ8.55 (triplet) due to an ethoxyl group in the compound (131a) is consistent with the aromatic splitting pattern in the ^{1}H n.m.r. spectrum which is characteristic of a 1,2,4-trisubstituted benzene derivative. The presence of the N-acetoxy group was shown by the singlet at τ7.50 in the ^{1}H n.m.r. spectrum and this was confirmed by the presence of an absorption band in the i.r. spectrum at 1795 cm^{-1} which is characteristic of a cyclic N-acetoxy group.[43] The mass spectrum and analytical data were also consistent with the structure (131a). As in the previous cases, the evidence cited does not exclude the possibility that the substituent is in the 6-position.

The mother liquors from the reaction of the perchlorate (107a)

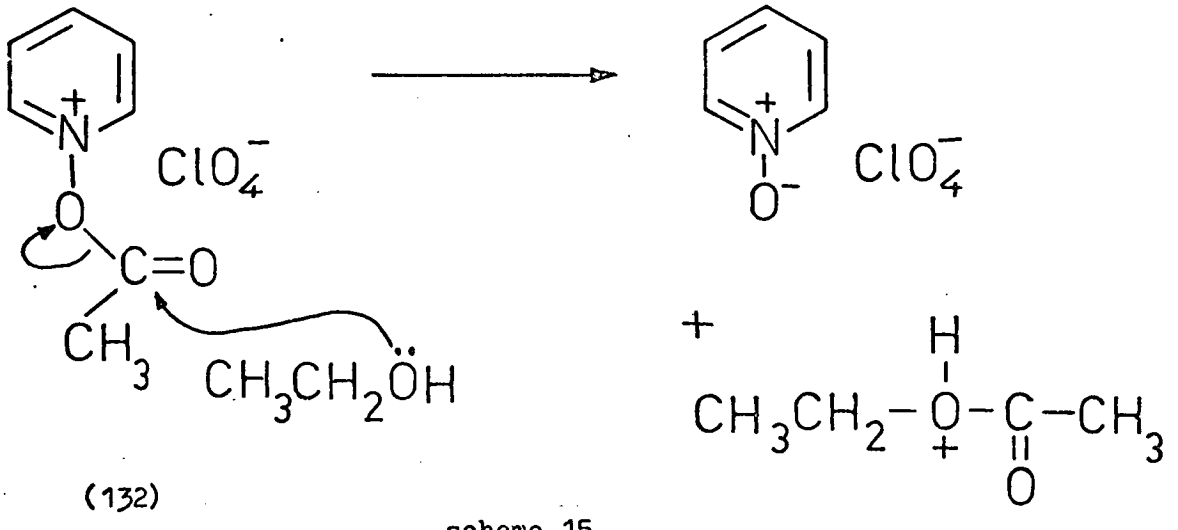
with ethanol afforded a moderate yield of a product which is assigned the structure (131b). The ^{1}H n.m.r. spectrum of the product showed peaks at τ 5.80 (quartet) and τ 8.52 (triplet) due to an ethoxyl group which was shown to be in the 7-position by the fact that H-5 appears as a doublet with a coupling constant of 9.0 Hz. The signals due to H-6 and H-8 overlapped and therefore the full splitting pattern for a 1,2,4-trisubstituted benzene derivative was not observed. The fact that the N-acetoxy group in the perchlorate (107a) had been hydrolysed to an N-hydroxyl group during the reaction was indicated by the absence of a peak at 1795 cm^{-1} in the i.r. spectrum of the product (131b) and the presence of a broad absorption at 3100 - 2600 cm^{-1}. The presence of the N-hydroxyl group in the product (131b) was confirmed by the production of a deep red colour with ferric chloride in ethanol.[43] The mass spectrum and analytical data were also consistent with the 7-ethoxy structure (131b). The perchlorate (107a) also reacted with methanol to give moderate yields of the 1-N-acetoxy-7-methoxy derivative (131c) and the 7-methoxy-1-N-hydroxy derivative (131d). The structures of these products were confirmed exactly as for the compounds (131 a and b).

In order to study the effect of a substituent at C-7, the quinoxalinium perchlorate (107b) was prepared and was reacted with ethanol. The first product isolated from the reaction mixture in moderate yield was shown to contain an ethoxyl group by its ^{1}H n.m.r. spectrum, which contained a quartet at τ 5.73 and a triplet at τ 8.40. The fact that the ^{1}H n.m.r. spectrum contained an absorption at τ 7.38, attributable to a C-methyl group, indicated that the ethanol had attacked the benzene ring of the perchlorate (107b). The product is assigned the 5-ethoxy structure

(131e) on the assumption that the 5-position is the one most susceptible to nucleophilic attack when the 7-position is blocked. The ^{1}H n.m.r. spectrum was in accord with this structure although the aromatic protons overlapped and the position of the ethoxyl group could not be proved unequivocally by analysis of the aromatic splitting pattern. The presence of the N-hydroxyl group was confirmed by the presence of broad absorption in the i.r. spectrum of (131e) at 3200 cm^{-1} and by the production of a deep red colour with ferric chloride in ethanol.[43] The mass spectral and analytical data were also fully in accord with the structure (131e).

The mother liquors from the reaction of the perchlorate (107b) with ethanol gave a moderate yield of a second product which was shown to be the 7-ethoxymethyl derivative (131f) from its spectral properties. The fact that the ethanol had attacked the 7-methyl group was shown by the presence of a peak corresponding to a methylene group at τ 4.96 in the ^{1}H n.m.r. spectrum. The i.r. and mass spectra and the analytical data were all fully in accord with the structure (131f), and the compound also gave a deep red colour with ferric chloride in ethanol.

There are relatively few examples of reactions of N-acetoxy

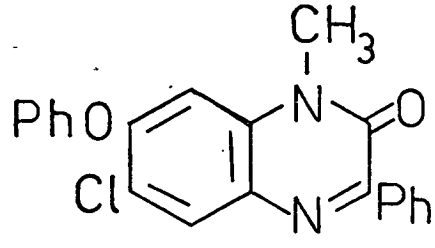


(132)

scheme 15

perchlorates with alcohols. It has been shown[10] (scheme 15) however that N-acetoxypyridinium perchlorate (132) undergoes attack by hot ethanol at the N-acetoxy group to give pyridine N-oxide and protonated ethyl acetate.

The reaction of the perchlorate (105b) with phenol in dry ether did not give the product (133) in which phenol has attacked



(133)

the perchlorate at the 7-position. Thus phenol is a much poorer nucleophile in these reactions than are alcohols.

2.6 The Reactions of Quinoxalinium Perchlorates with Amines

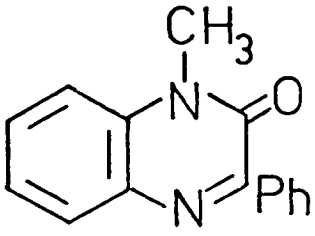
As mentioned in the introduction (chapter one), amines are generally not sufficiently nucleophilic to attack heterocyclic N-oxides unless the N-oxide group is in the form of a quaternary cation (82) or an adduct with a Lewis Acid (83). Since the perchlorates (105) have been shown to react with nucleophiles such as anions, water and alcohols, it was of interest to study the reactions of these perchlorates with various amines.

These reactions were complicated by the fact that a suitable medium in which to carry out the reactions proved difficult to find. Reaction of the perchlorate with the neat amine was not entirely satisfactory since reactions of this type invariably produced black tars which had to be purified by column chromatography. As discussed previously in this chapter, the perchlorates (105) tended to decompose in organic solvents, and it was therefore difficult to carry out the reaction with amines in solution. Acetonitrile was used as the solvent in some of the early reactions but it was subsequently shown that the perchlorates (105) decomposed in this solvent. Consequently, later reactions with amines were carried out on suspensions of the perchlorates (105) in dry ether or by reacting the perchlorates with the neat amines and separating the gums obtained by column chromatography.

I. Primary Amines

All of the reactions of the perchlorates (105) with primary amines were carried out using acetonitrile as the solvent. The perchlorate (105a) reacted with methylamine in acetonitrile to give moderate yields of the corresponding N-oxide (104a) and the deoxygenated derivative (110a)[46], and a low yield of the 7-hydroxy

compound (115h). The reaction of the perchlorate (105a) with



(110a)

ethylamine in acetonitrile gave a similar result except that the yield of the N-oxide (104a) was much lower than in the methylamine reaction. The structures of the products (104a), (110a) and (115h) were confirmed by comparison with authentic samples.[14] The perchlorate (105b) also reacted with aniline and ethylamine to give moderate yields of the N-oxide (104b), the deoxygenated compound (110b) and the 7-hydroxy compound (115g), the structures of which were again confirmed by comparison with authentic samples.[14]

In order to find out whether an N-unsubstituted perchlorate would react with a primary amine, the perchlorate (105g) was reacted with ethylamine in acetonitrile. The product isolated in good yield was the corresponding N-oxide (104g), the structure of which was confirmed by comparison with an authentic sample.[14]

Thus, in the reactions of the perchlorates (105) with primary amines, no products were isolated which corresponded to attack at the 7-position of the perchlorate by the amine. The mechanism of the formation of the deoxygenated compounds (110 a and b) is not clear. The fate of the oxygen atom originally bonded to N-4 in the perchlorates (105 a and b) was not discovered. A similar result

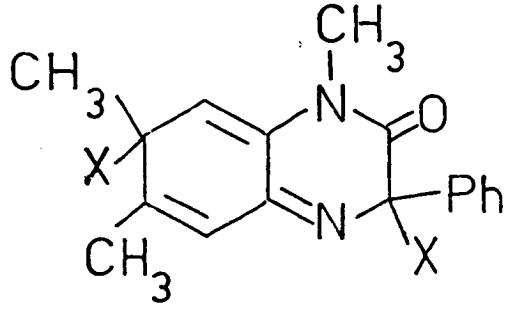
was obtained when the perchlorate (105b) reacted with acetonitrile alone (page 27). The 7-hydroxy compounds (115 g and h) are presumably formed by reaction of the perchlorates (105 b and a) respectively with traces of water in the reaction mixture. The N-oxides (104 a, b and g) could be formed by solvolysis of the N-acetoxy group in the perchlorates (105 a, b and g). However the fate of the acetyl group derived from solvolysis of the N-acetoxy group was not established.

II. Secondary Amines

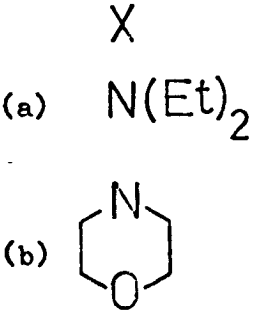
1(a) Diethylamine as Solvent

The perchlorate (105a) reacted with neat diethylamine to give a low yield of a product whose spectral properties indicated that it was the 7-diethylamino derivative (134a). The ^{1}H n.m.r. spectrum of the product showed the presence of one diethylamino group and the fact that it was in the 7-position was indicated by the characteristic splitting pattern of the H-5, H-6 and H-8 aromatic protons. The mass spectrum and analytical data were also consistent with the structure (134a). A moderate yield of the 7-hydroxy compound (115h) was also obtained in this reaction, probably due to reaction of the perchlorate (105a) with traces of water.

The effect of a substituent in the 7-position was studied by reacting the perchlorate (105e) with diethylamine. The product isolated from this reaction in moderate yield is assigned the structure (135a). The ^{1}H n.m.r. spectrum of the adduct (135a) showed

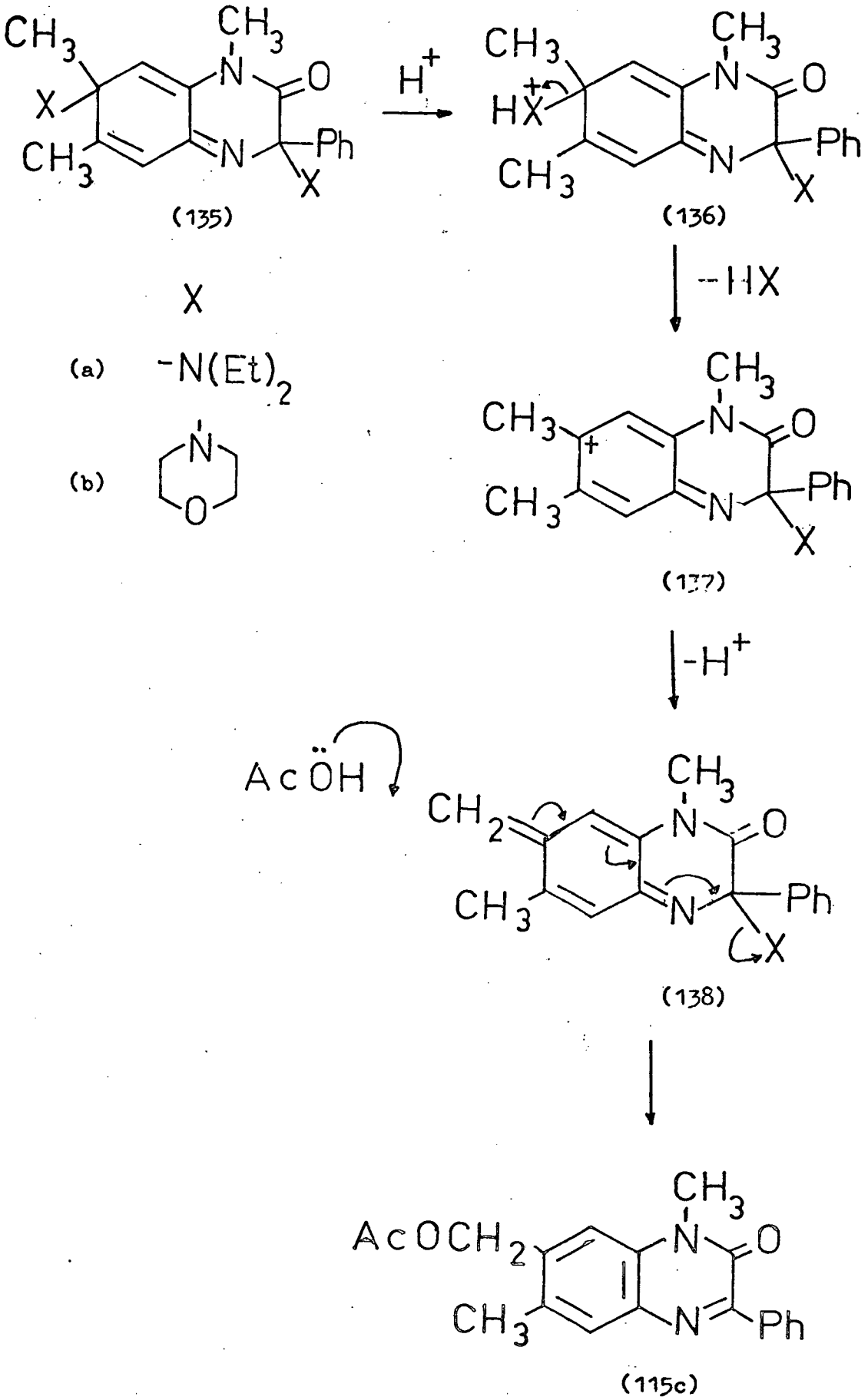


(135)

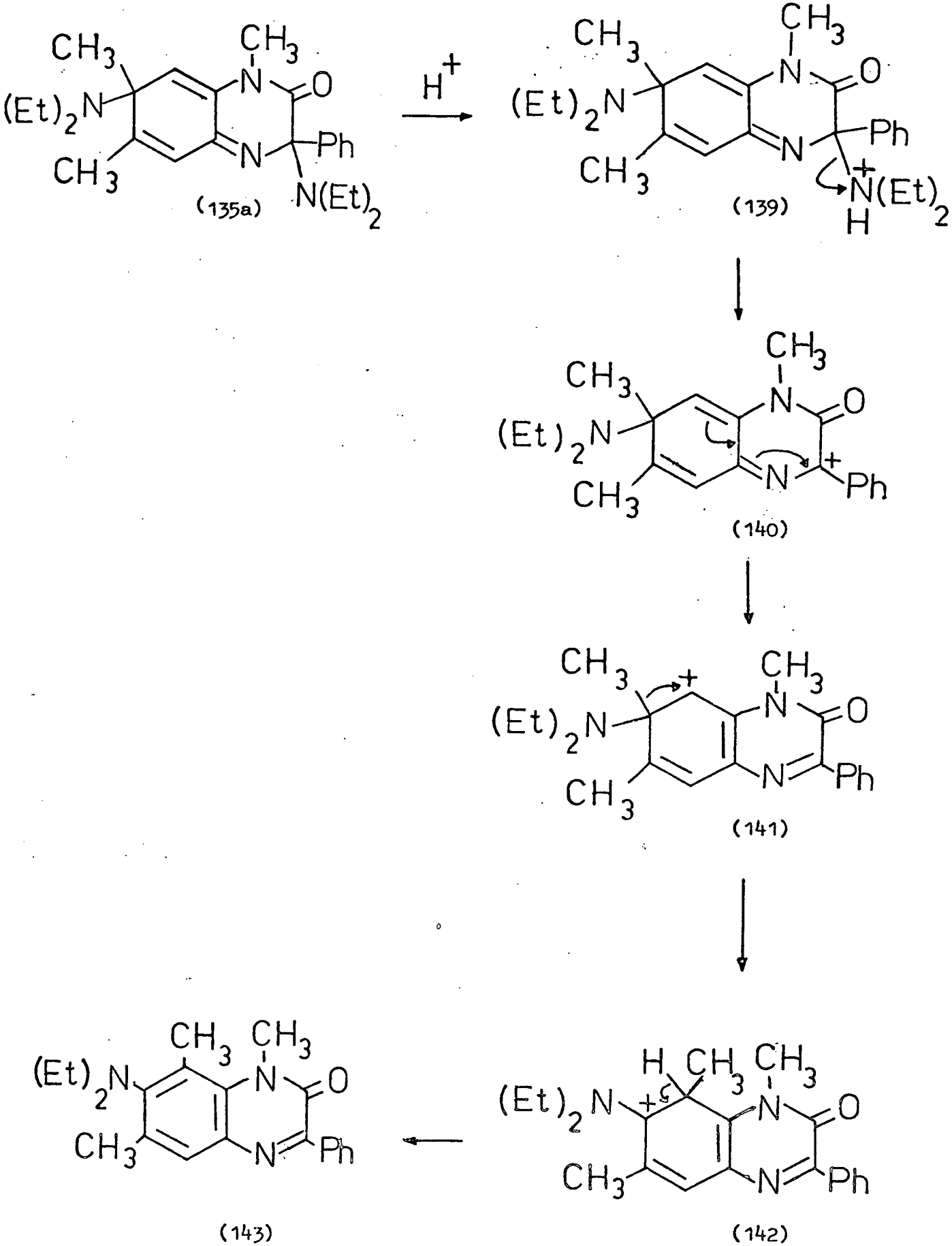


the presence of two diethylamino groups in the molecule and also contained olefinic absorptions, [a multiplet at τ 3.66 (1H) and a doublet at τ 4.53 (1H)]. Spin decoupling showed that the C-methyl group at the 6-position (τ 8.02) is coupled to the H-5 olefinic proton at τ 3.66. The doublet at τ 8.02 collapsed to a singlet on irradiation at τ 3.66. However, irradiation at τ 8.02 caused the multiplet at τ 3.66 to collapse to a doublet. This suggests that the product from the reaction may be a mixture of stereoisomers since there is no single proton present in the molecule with which H-5 could couple and thus show up in the ^{1}H n.m.r. spectrum as a doublet. The suggestion that the product is an isomer mixture is supported by the fact that the N-methyl signal at τ 6.92 in the ^{1}H n.m.r. spectrum is also a doublet. The only proton with which the N-methyl group could couple is H-8 and this proton is rather far away from the N-methyl group to be coupled with it. The Stereoisomeric forms of the adduct (135a) could arise due to the fact that the 7- and 3- positions in the molecule are asymmetric centres. The analytical data for the product was consistent with structure (135a). The i.r. spectrum showed carbonyl absorption at 1670 cm^{-1} which is slightly low for the structure (135a) in which the carbonyl group is unconjugated. The highest peak in the mass spectrum of the product occurs at 336 mass units. The molecular weight of the adduct (135a) is 408 and the peak at 336 mass units in the mass spectrum can be attributed to the stable carbonium ion (137a) (molecular weight 336) (*cf.* scheme 16).

Further evidence to support the suggestion that the adduct (135a) is an isomer mixture was obtained by the reaction of (135a) with glacial acetic acid to give a high yield of a single compound,


CH3
CH3
N
O
X
CH3
N
Ph
X
(135)
H+
CH3
CH3
N
O
HX+
CH3
N
Ph
X
(136)
X
(a) -N(Et)2
(b)
N
O
-HX
CH3
CH3
N
O
+
CH3
N
Ph
X
(137)
-H+
AcÖH
CH3
CH2
N
O
CH3
N
Ph
X
(138)
CH3
AcOCH2
N
O
CH3
N
Ph
(115c)

scheme 16



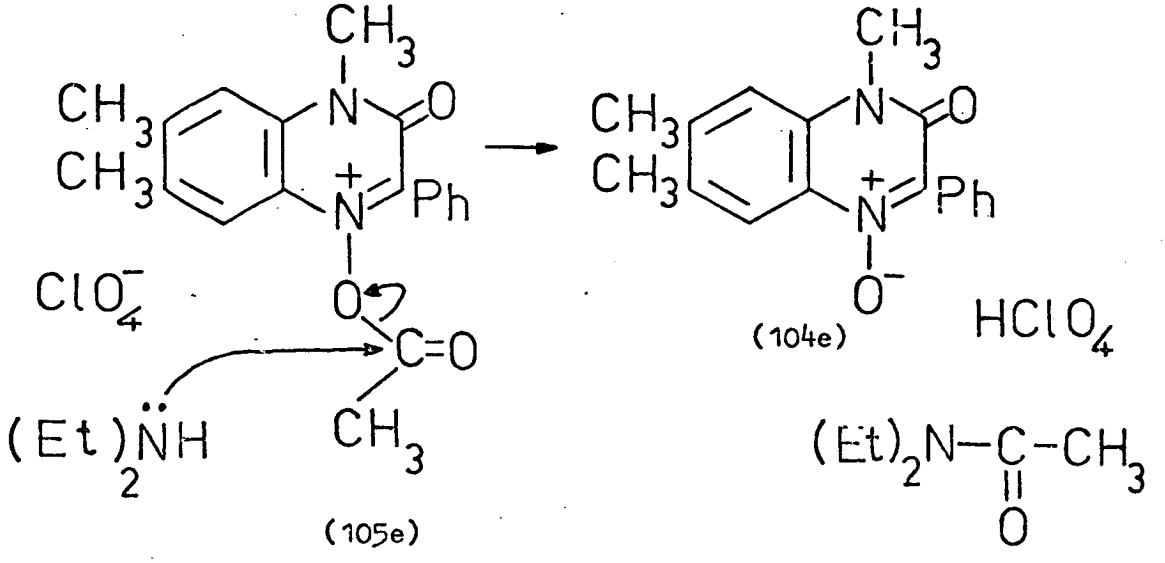
scheme 17

the 7-acetoxymethyl derivative (115c). The mechanism suggested for this reaction is outlined in scheme 16. Protonation of the 7-diethylamino group gives the intermediate (136a) which can then eliminate diethylamine to give the carbonium ion (137a). Elimination of a proton from the carbonium ion (137a) gives the intermediate (138a) which undergoes nucleophilic attack by acetic acid at the 7-methylene group to give the observed product (115c).

The adduct (135a) was also found to react with aqueous hydrochloric acid to give a high yield of a single compound which is tentatively assigned the 7-diethylamino structure (143) as shown in scheme 17. In this scheme, protonation in the strong aqueous acid takes place at the 3-diethylamino group to give the intermediate (139) which eliminates diethylamine to give the carbonium ion (140) which is tautomeric with (141). The carbonium ion (141) then undergoes a methyl shift to afford the intermediate (142) which eliminates a proton giving the observed product (143). The ^{1}H n.m.r. spectrum of the product was consistent with the assigned structure (143). The spectrum showed the presence of one diethylamino group in the molecule and there were six aromatic protons, one of which, H-5, was a singlet. The ^{1}H n.m.r. spectrum of (143) lacked benzylic absorption and showed the presence of three methyl groups which indicated that attack had not taken place at any of the methyl groups.

The conversion of the adduct (135a) into the 7-diethylamino compound (143) by aqueous hydrochloric acid explains why the compound (143) was isolated from the aqueous washings in one case when the perchlorate (105c) was reacted with diethylamine. The initial product from the reaction is the adduct (135a) which is

converted by the aqueous hydrochloric acid into the 7-diethylamimo compound (143). The only other product isolated from the last reaction was a moderate yield of the N-oxide (104e) which could be formed by attack at the N-acetoxy group by the amine. (scheme 18).



scheme 18

However the N,N-diethylacetamide formed as a by product was not detected in the reaction mixture.

When the perchlorate (105j) was reacted with diethylamine, a high yield of the corresponding N-oxide (104j) was obtained. The N-oxide (104j) is again presumably formed by nucleophilic attack at the N-acetoxy group (cf. scheme 18).

The perchlorate (105f) reacted with diethylamine to give a low yield of a product which was shown to be the 7-diethylamino compound (134c). The ^{1}H n.m.r. spectrum showed the presence of a diethylamino group and the characteristic splitting pattern of the aromatic protons in the spectrum indicated that substitution had taken place in the 7-position. The i.r. and mass spectra, and the analytical data were also fully in accord with structure (134c). The main product from the

reaction of the perchlorate (105f) with diethylamine was however the N-oxide (104f).

The reaction of the perchlorate (107a) with diethylamine produced a black intractable tar. No attempt was made to separate this tar by column chromatography because it was anticipated that the 1-N-acetoxy group present in the starting material (107a) would be hydrolysed on the column to an acidic N-hydroxyl group which would not elute from the column.

1(b) Diethylamine in Acetonitrile

The perchlorates (105 a and b) reacted with diethylamine in acetonitrile to give moderate yields of the 7-diethylamino compounds (134 a and b) respectively. The structure of compound (134b) was confirmed by comparison with a sample obtained previously. The structure of compound (134a) was supported by its spectral properties. The ^{1}H n.m.r. spectrum indicated the presence of a diethylamino group which was shown to be in the 7-position by the characteristic splitting pattern of the aromatic protons. The i.r. and mass spectra, and the analytical data were also fully in accord with the structure (134a). The other products isolated in moderate yield from these two reactions were the N-oxides (104 a and b) and the 7-hydroxy compounds (115 h and g) which were characterised by comparison with samples obtained previously.

The fact that no deoxygenated compounds (110 a and b) were obtained in these reactions indicates that the diethylamine must be reacting with the perchlorates (105 a and b) before they are decomposed by the acetonitrile. Thus the N-oxides (104 a and b) are formed by attack at the N-acetoxy group in the perchlorates (105 a and b) by the diethylamine. The 7-hydroxy compounds (115 h

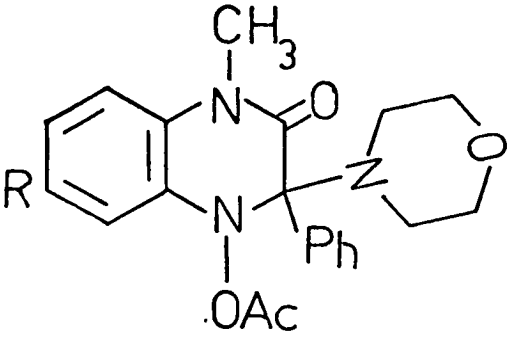
and g) could be formed by attack on the perchlorates (105 a and b) by water present in the reaction mixture.

1(c) Diethylamine in Ether

When the perchlorate (105b) was reacted with diethylamine in ether, low yields of the deoxygenated compound (110b), the N-oxide (104b), the 7-diethylamino derivative (134b) and the 7-hydroxy derivative (115g) were obtained. All of these compounds were characterised by comparison with authentic samples. An unidentified solid was also obtained in this reaction which appeared to be a salt and could be diethylamine perchlorate. The formation of the N-oxide (104b), the 7-diethylamino derivative (134b) and the 7-hydroxy derivative (115g) in this reaction can le explained in the same way as for the reaction of the perchlorate (105b) with diethylamine in acetonitrile. As mentioned before, the formation of the deoxygenated compound (110b) is more difficult to rationalise.

2. Morpholine

The perchlorates (105 a and b) reacted with morpholine in ether to give moderate yields of products which are assigned the structures (144 a and b) respectively. The presence of the N-acetoxy group



R	(144)
H	(a)
Cl	(b)

in the molecules (144 a and b) was shown by the presence of an absorption band at 1790 cm^{-1} in the i.r. spectrum which is characteristic of a cyclic N-acetoxy group.[43] The ^{1}H n.m.r. spectra of the products were consistent with structures (144 a and b). The mass spectra of (144 a and b) however did not contain peaks corresponding to the parent ions derived from the adducts (144 a and b). The highest peaks in the mass spectra occurred at M-60 which corresponds to the loss of the elements of acetic acid from the adducts (144 a and b). Analytical data for compounds (144 a and b) could not be obtained because the compounds were unstable and could not be crystallised.

The mother liquors from the reactions leading to the adducts (144 a and b) gave low yields of the corresponding N-oxides (104 a and b), the deoxygenated compounds (110 a and b) and the 7-hydroxy compounds (115 h and g).

The adduct (144b) was found to react with 99% ethanol to give a good yield of the 7-ethoxy compound (126c) and a moderate yield of the 7-hydroxy compound (115g). The structures of these two products were confirmed by comparison with authentic samples.

The adduct (144b) also reacted with glacial acetic acid to give a high yield of the 7-acetoxy compound (115b) and with aqueous hydrochloric acid to give a high yield of the 6,7-dichloro compound (115j). These last two products were characterised by comparison with authentic samples.

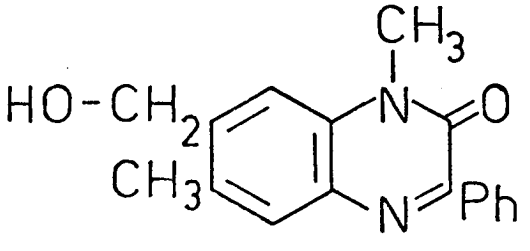
The mechanisms of the formation of the adducts (144 a and b) and the reactions of the adduct (144b) with ethanol, glacial acetic acid and aqueous hydrochloric acid will be discussed later.

The perchlorate (105e) reacted with morpholine in ether to give a moderate yield of a product which is assigned the structure (135b).

The ^1H n.m.r. spectrum of the adduct (135b) showed the presence of two morpholine residues in the molecule, and also contained signals due to two olefinic protons. The proton at τ 3.60 could be shown to be coupled to the C-methyl group at τ 8.03. Irradiation at τ 3.60 caused the doublet at τ 8.03 to collapse to a singlet and irradiation at τ 8.03 caused the quartet at τ 3.60 to collapse to a singlet. The nature of this coupling suggests that the proton at τ 3.60 is the H-5 proton and the C-methyl group at τ 8.03 is the 6-methyl group. On expansion to sweep width 250 Hz, slight multiplicity appeared in the quartet at τ 3.60. This could either be due to long range coupling or it could indicate that the adduct (135b) is an isomer mixture. The i.r. spectrum and the analysis of the morpholine adduct were fully in accord with structure (135b). The mass spectrum of the compound showed a peak at 436 mass units corresponding to the molecular weight of (135b). There was however a very strong peak in the mass spectrum at 350 mass units which corresponds to the carbonium ion (137b) (scheme 16).

Further evidence to support the structure of the adduct (135b) was provided by the conversion of the adduct (135b) in glacial acetic acid into the 7-acetoxymethyl derivative (115c) in high yield as shown in scheme 16.

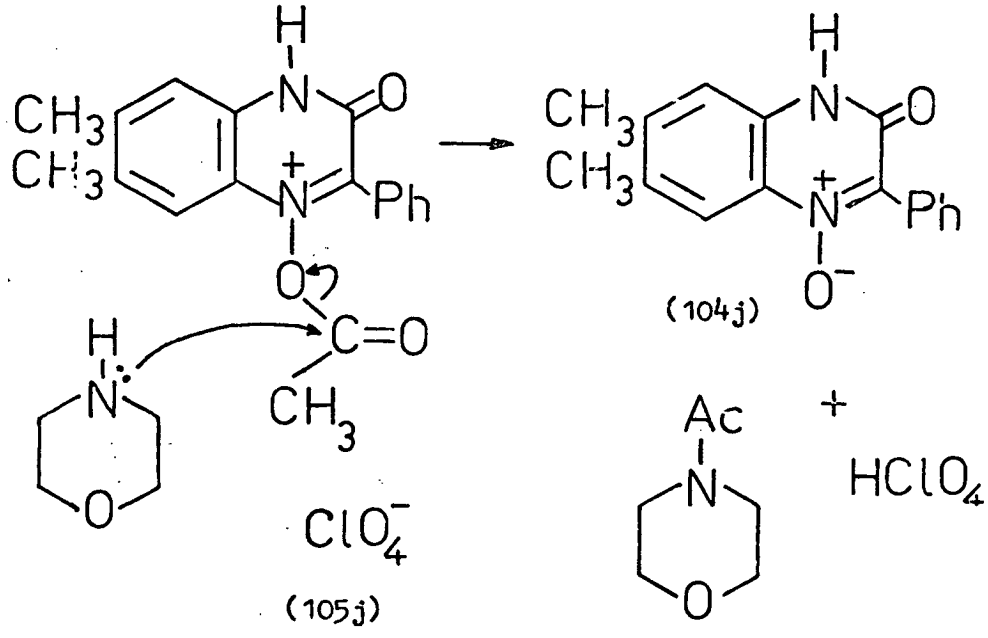
The reaction of the perchlorate (105e) with morpholine also produced a moderate yield of the N-oxide (104e) and a trace of the hydroxymethyl derivative (115d). The hydroxymethyl derivative (115d)



(115d)

could be formed by attack by water on the perchlorate (105e) or possibly on the adduct (135b) since the adduct has also been shown to undergo nucleophilic substitution at the 7-methyl group (*cf.* 135b → 115c) (scheme 16).

When the perchlorate (105j) was reacted with morpholine, the only product obtained in good yield was the corresponding N-oxide (104j). Thus in this case the morpholine attacks the acetoxy group rather than the 2- or 7-position in the perchlorate (scheme 19). The N-acetylmorpholine was not isolated in the reaction possibly



scheme 19

because it is volatile and is lost in the work up.

The reason for the difference in reactivity between the perchlorates (105 e and j) in the reactions with morpholine could be due to the lower reactivity (to initial nucleophilic attack) at the 2-position in the perchlorate (105j) compared with the perchlorate (105e).

3. Pyrrolidine

Reaction of the perchlorate (105b) with pyrrolidine in acetonitrile gave moderate yields of the N-oxide (104b), the deoxygenated compound (110b) and the 7-hydroxy compound (115g) which were characterised by comparison with authentic samples. No product corresponding to attack by pyrrolidine at the 7-position of the perchlorate (105b) was isolated from the reaction.

Since it was found that the perchlorate (105b) decomposed in acetonitrile, the reaction of (105b) with pyrrolidine in ether was also carried out. This reaction gave moderate yields of the N-oxide (104b) and the 6,7-dichloro compound (115j), and a small amount of the 7-hydroxy compound (115g). These products were identified by comparison with authentic samples. The reaction was worked up with aqueous hydrochloric acid and it is possible that the dichloro compound is being formed by nucleophilic attack on unreacted perchlorate (105b) by chloride ion. Another possibility is that the pyrrolidine is forming an adduct similar to that obtained in the diethylamine and morpholine reactions [cf. (135 a and b)] which is reacting with the hydrochloric acid to give the dichloro compound (115j).

III Tertiary Amines

(a) Triethylamine

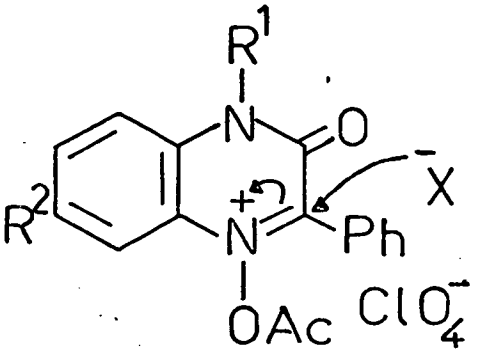
The perchlorate (105b) reacted with triethylamine in acetonitrile to give a good yield of the N-oxide (104b) and low yields of the deoxygenated compound (110b) and the 7-hydroxy compound (115g). These products were all characterised by comparison with authentic samples. The fact that a good yield of the N-oxide (104b) was obtained suggests that the triethylamine is attacking the N-acetoxy

group in the perchlorate (105b) as described previously (cf. scheme 19).

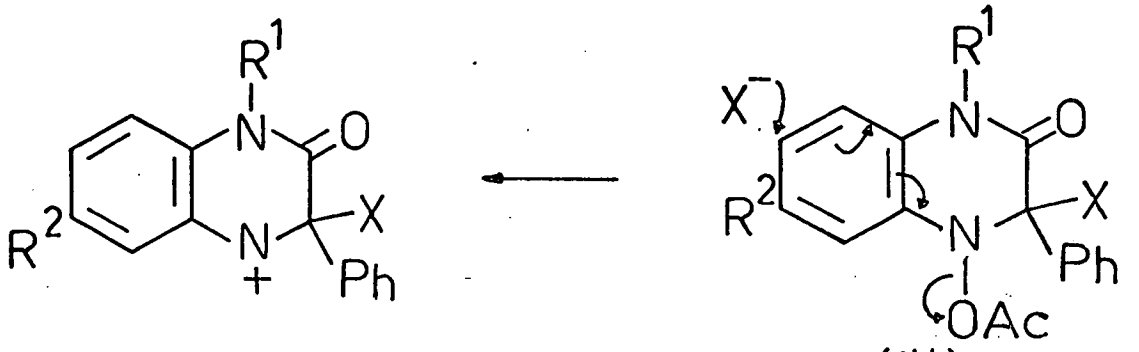
(b) Pyridine

The perchlorate (105b) reacted with pyridine in a similar way to triethylamine to give a high yield of the N-oxide (104b).

X = OAc
Cl
NCS
CN
OH
OCH_3
OEt^3
OisoPr
$N(Et)_2$

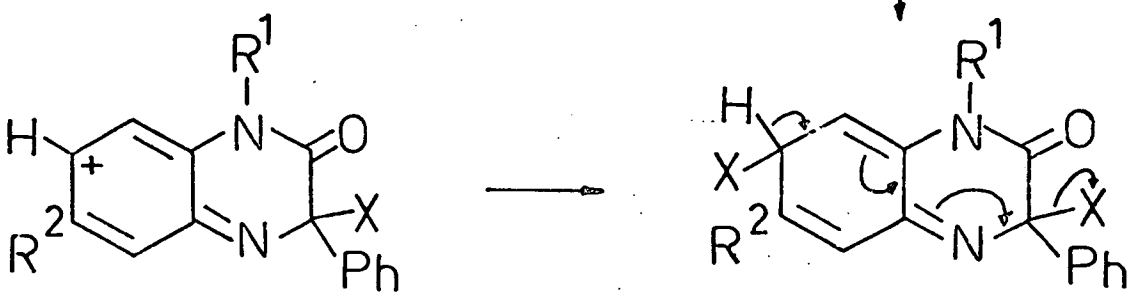


(105 a-d and f-i)



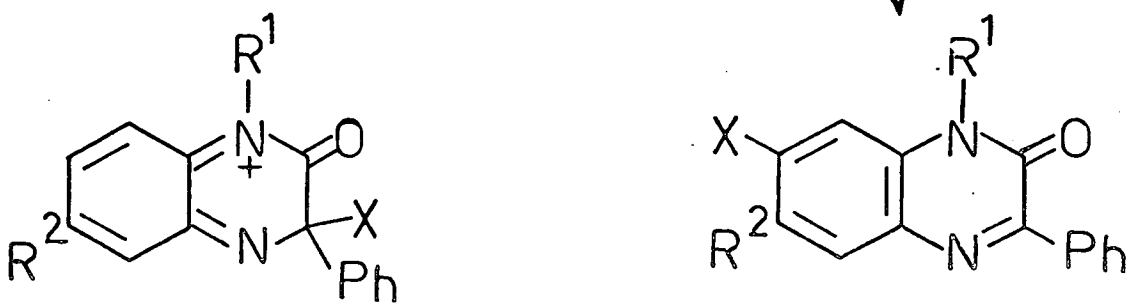
(144)

$- OAc^-$



(146)

- HX



(145)

(147)

scheme 20

2.7 Discussion of Reaction Mechanisms

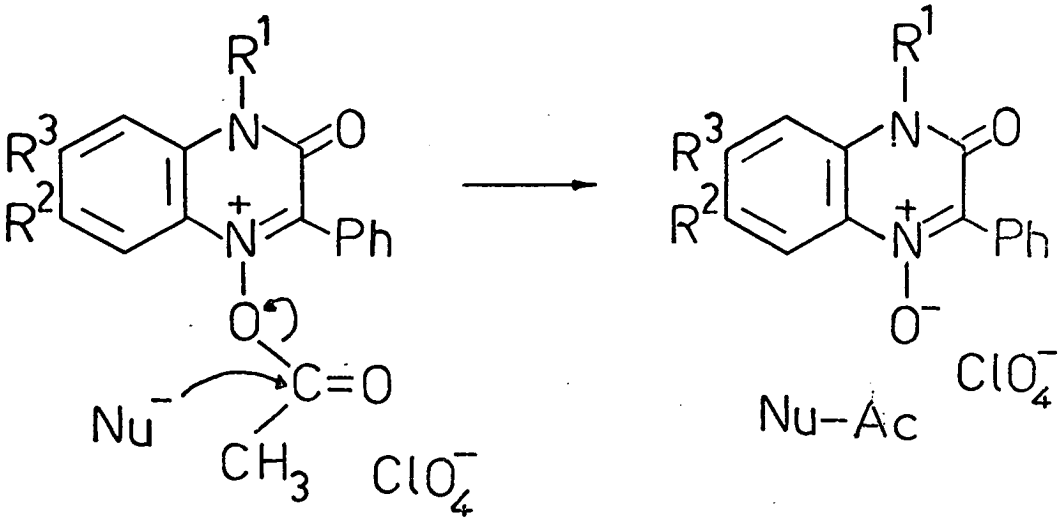
The reactions of the perchlorates (105) with nucleophiles are explicable by the mechanism outlined in scheme 20. The perchlorates (105) undergo nucleophilic attack by X^- at the 3-position to give the adducts (144) which can undergo simultaneous attack by X^- at the 7-position and loss of the N-acetoxy leaving group giving the para-quinoid intermediates (146). Elimination of HX from the intermediates (146) gives the observed products (147) [(144)→(146)→(147)].

Alternatively, the adducts (144) could eliminate the N-acetoxy leaving group to form the resonance stabilised nitrenium cation intermediates (145). Nucleophilic attack by X^- at the 7-position of the intermediates (145) gives the para-quinoid intermediates (146) which give the observed products as described above [(144)→(145)→(146)→(147)]. Nitrenium cations have been suggested as intermediates in the substitution reactions[47] of certain five-membered N-oxygenated benzaza heterocycles. The intermediates (145) should show enhanced stability due to the resonance stabilisation as shown in scheme 20. The mechanism outlined in scheme 20 accounts for the formation of the 7-substituted products in the reaction of the perchlorates (105 a-d and f-i) with anions, water, alcohols and amines.

The reaction of the N-oxide (104a) with hot acetic anhydride[14] to give the acetoxy compound (115a) can also be rationalised in terms of the mechanism outlined in scheme 20.

As mentioned earlier, the perchlorates (105) can also undergo nucleophilic attack at the N-acetoxy group to give the corresponding

N-oxide (104) (scheme 21). The acetylated nucleophile (Nu-Ac) was

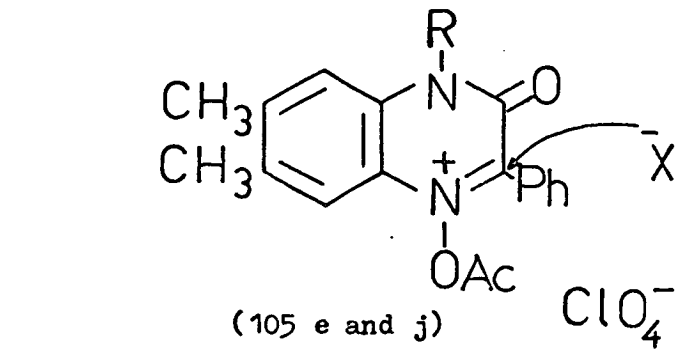


(105) (104)

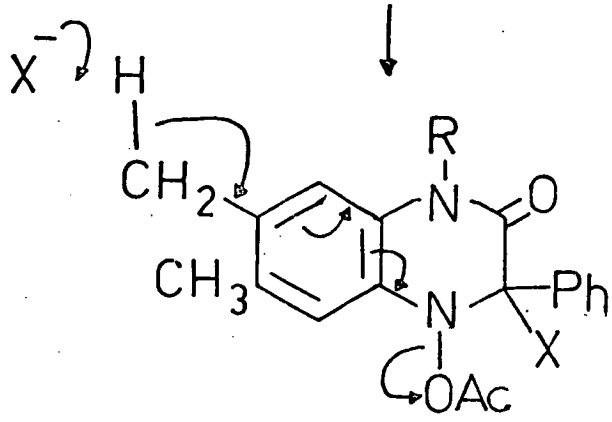
scheme 21

not isolated in any of these reactions probably because it was volatile and was evaporated from the reaction mixture on work up or because it was soluble in water and was removed when the extracts were washed with water.

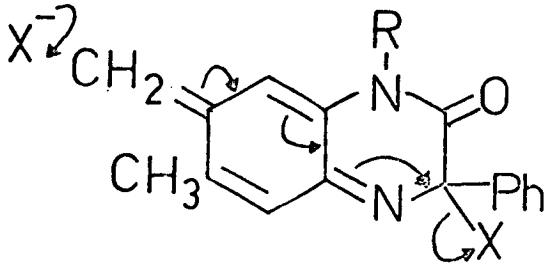
The formation of the adducts (140 a and b) is also explicable by the mechanism outlined in scheme 20. Morpholine attacks the perchlorates (105 a and b) at the 3-position as shown in scheme 20 giving the adducts [(144 a and b), X = morpholino]. In the case of morpholine, the adducts (144) appear to be less reactive towards nucleophilic substitution and are thus more stable and can be isolated providing good evidence for the mechanism shown in scheme 20. The mechanism in scheme 20 is also substantiated by the fact that the morpholine adduct (144b) undergoes nucleophilic substitution at the 7-position when reacted with ethanol, glacial acetic acid and aqueous hydrochloric acid giving the 7-ethoxy compound (126c), the 7-acetoxy compound (115b) and the 7-chloro compound (115j) respectively.



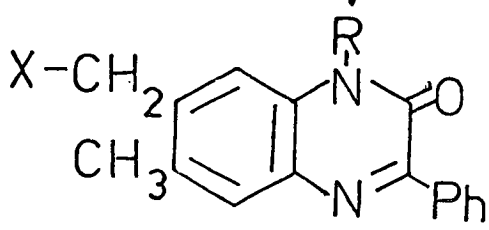
(105 e and j)



(148)



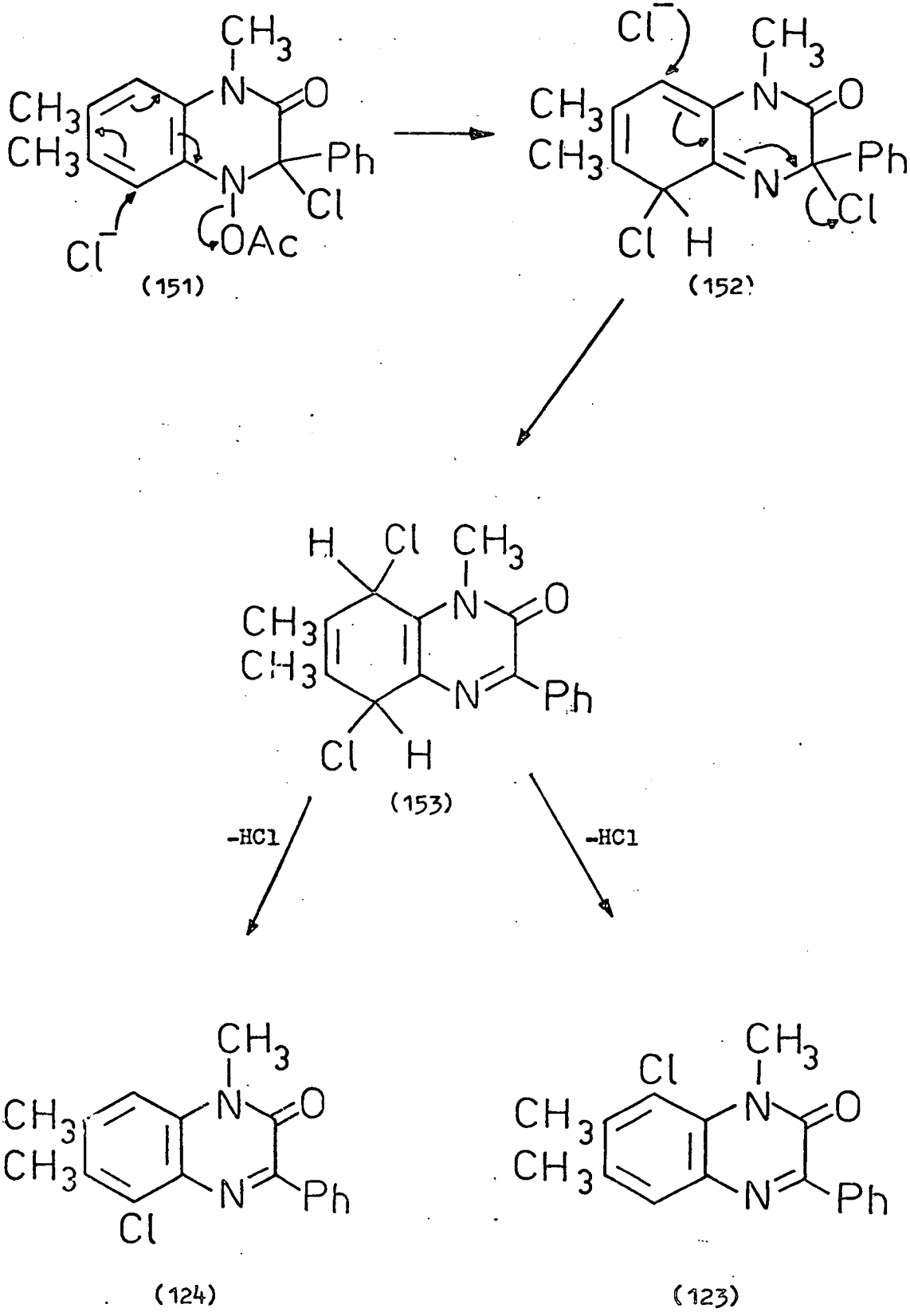
(149)



(150)

Perchlorate	R	Nucleophile	X
(105e)	CH_3		OAc, OEt, OCH_3
(105j)	H		OAc, OEt

scheme 22



scheme 23

The differences in reactivity in the reactions of the N-methyl perchlorate (105a) and the N-unsubstituted perchlorate (105f) (e.g. reaction with acetate ion) could be due to differences in the basicity of the 1-nitrogen. This could cause differences in the stability of the nitrenium cation (145) (scheme 20). If the nitrenium cation is less stable in the N-unsubstituted case, then nucleophilic attack could take place at the N-acetoxy group rather than at the ring.

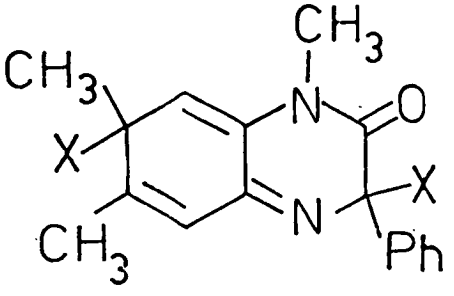
The reactions of the perchlorate (105e) can be explained by the mechanism outlined in scheme 22.[39] The perchlorates (105 e and j) undergo nucleophilic attack by X^- at the 3-position to give the intermediates (148) which eliminate the elements of acetic acid to afford the intermediates (149). Nucleophilic attack by X^- at the methylene centre in structure (149) with simultaneous loss of X^- from the 3-position gives the observed products (150).

The mechanism outlined in scheme 22 however does not explain why the perchlorate (105j) reacts with methanol to give a product (129) in which the methoxyl group appears to be in the 5-position. In the reaction of the perchlorate (105e) with lithium chloride to give low yields of the 5- and 8-chloro derivatives (124) and (123), chloride ion is not a strong enough base to effect the step (148 → 149) in scheme 22 and chloride ion therefore attacks the ring.

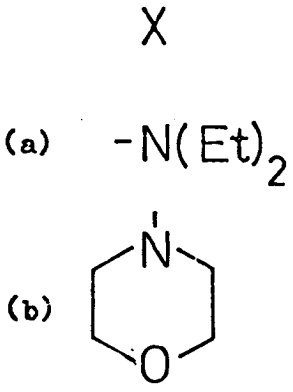
A mechanism which explains the formation of the 5- and 8-chloro derivatives (124) and (123) is outlined in scheme 23. The intermediate (151) [cf. (144), scheme 20] undergoes nucleophilic attack by chloride ion at the 5-position with simultaneous loss of the acetoxy group from the 4-position giving the intermediate (152). Nucleophilic attack by chloride ion at the 8-position of the

intermediate (152) gives the 5,8-dichloro intermediate (153). Elimination of hydrogen chloride from the dichloro intermediate (153) gives the 5- and 8-chloro derivatives (124) and (123). However in the absence of firm experimental evidence the mechanism shown in scheme 23 must remain at present only a tentative suggestion.

The formation of the adducts (135 a and b) can be explained by a mechanism analogous to that shown in scheme 20. The para-quinoid intermediates [(146), scheme 20] derived from the 7-unsubstituted



(135)



perchlorates (105 a-d and f-i) can be stabilised by aromatisation by the elimination of HX. In contrast, the adducts (135) cannot be stabilised in this way since there is not a proton at the 7-position. The adducts (135) therefore react by undergoing a methyl shift (scheme 17, page 54) or by protonation at the amino-group in the 7-position (scheme 16, page 54). Thus, the isolation of the adducts (135) is further evidence for the reaction mechanism shown in scheme 20.

The reactions of the perchlorates (107a) and (107b) with nucleophiles can likewise be explained by mechanisms analogous to those shown in schemes 20 and 22 respectively.

Chapter Three

Experimental Section - Quinoxalinium Perchlorates

3.1 The Synthesis of N-Acetoxyquinoxalinium Perchlorates

General Method

Acetic anhydride (2.0 ml) was cooled in an ice bath and treated dropwise with stirring with 60% w/w aqueous perchloric acid (0.6 ml) at such a rate that the temperature did not rise above 20°C.

The perchloric acid - acetic anhydride solution was then added dropwise with stirring to an ice-cooled suspension of the quinoxaline N-oxide (104) or (106) in glacial acetic acid (3.0 ml) and acetic anhydride (6.0 ml). The resulting red solution was stirred in the ice bath for 1 h and the N-acetoxyquinoxalinium perchlorate (105) or (107) which crystallised from the reaction mixture was collected by filtration, washed thoroughly with dry ether and sucked dry. Yield 34-98%, ν_{max} 1845-1830 (cyclic $\overset{+}{N}$.OAc), τ ($CF_3.CO_2H$) 7.75-7.80 (3H, s, N.OAc).

The N-acetoxyquinoxalinium perchlorates (105) and (107) were relatively stable in the absence of air and light but under normal conditions they tended to decompose to intractable brown gums. Consequently, the quinoxalinium perchlorates were used directly in subsequent reactions without purification.

The yields quoted in the reactions of the quinoxalinium perchlorates are based on the quantity of the corresponding N-oxide (104) or (106) used in their preparation.

The quantities of the N-oxide (104) or (106) described in this general method were used in the preparation of the perchlorates (105 a-j) and (107 a-c).

(a) 4-N-Acetoxy-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalinium perchlorate (105a) was prepared from 1-methyl-3-phenylquinoxalin-2(1H)-one 4-N-oxide (104a)[40] as a yellow crystalline solid (ca. 0.6 g) (ca. 76%), ν_{max} 1835 (cyclic $\overset{+}{N}$.OAc) cm^{-1}, τ ($CF_3.CO_2H$) 1.40-2.40 (9H, m, ArH), 5.93 (3H, s, N.CH_3) and 7.75 (*, s, $\overset{+}{N}$.OAc), $^m/e$ 294, M^+ (cation) 295.

* This signal integrated for more than three protons.

(b) 4-N-Acetoxy-6-chloro-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalinium perchlorate (105b) was prepared from the N-oxide (104b)[14] as a yellow crystalline solid (ca. 0.7 g) (ca. 81%), ν_{max} 1840 (cyclic $\overset{+}{N}$.OAc) cm^{-1}, τ ($CF_3.CO_2H$) 1.57 (1H, d, J_{meta} 2.5 Hz, H-5), 1.80-2.45 (7H, m, ArH), 5.98 (3H, s, N.CH_3) and 7.76 (3H, s, $\overset{+}{N}$.OAc).

The acetic acid - acetic anhydride mother liquors from the preparation of the salt (105b) were allowed to stand at room temperature for seven days. A yellow solid was deposited and was collected, washed with water and crystallised from ethanol - glacial acetic acid to yield the 7-acetoxy compound (115b) (0.10 g) (15%), m.p. 170° (lit.[14] 171°), identical (i.r. spectrum) with an authentic sample.[14]

(c) 4-N-Acetoxy-1,2-dihydro-1,6-dimethyl-2-oxo-3-phenylquinoxalinium perchlorate (105c) was prepared from the N-oxide (104c)[14] as a yellow crystalline solid (ca. 0.75 g) (ca. 91%), ν_{max} 1840 (cyclic $\overset{+}{N}$.OAc) cm^{-1}, τ ($CF_3.CO_2H$) 1.72 (1H, s, H-5), 1.98-2.31 (7H, m, ArH), 5.98 (3H, s, N.CH_3), 7.37 (3H, s, CH_3) and 7.79 (*, s, $\overset{+}{N}$.OAc).

(d) 4-N-Acetoxy-1,2-dihydro-6-methoxy-1-methyl-2-oxo-3-phenylquinoxalinium perchlorate (105d)

In the case of the N-oxide (104d)[14] the quinoxalinium perchlorate (105d) did not crystallise from the acetic acid - acetic anhydride

solution and this solution was therefore added dropwise with stirring to ice cold dry ether (200 ml). The quinoxalinium perchlorate (105d) was obtained as a red crystalline solid which on attempted filtration immediately decomposed to a brown gum.

Due to its instability, subsequent reactions of the perchlorate (105d) were carried out on a freshly prepared sample, washed by decantation with dry ether and handled as an ethereal suspension. It was not possible to obtain spectroscopic data for the perchlorate (105d) due to its instability.

(e) 4-N-Acetoxy-1,2-dihydro-2-oxo-3-phenyl-1,6,7-trimethyl quinoxalinium perchlorate (105e) was prepared from the N-oxide (104e)[39] as a yellow crystalline solid (ca. 0.75 g) (ca. 91%), ν_{max} 1840 (cyclic $\overset{+}{N}$.OAc) cm^{-1}, τ ($CF_3.CO_2H$) 1.78 (1H, s, H-5), 2.04-2.54 (6H, m, ArH), 5.99 (3H, s, $N.CH_3$), 7.38 (3H, s, CH_3), 7.46 (3H, s, CH_3) and 7.80 (*, s, $\overset{+}{N}$.OAc).

(f) 4-N-Acetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium perchlorate (105f) was prepared from the N-oxide (104f)[40] as a yellow crystalline solid (ca. 0.75 g) (ca. 95%), ν_{max} 1840 (cyclic $\overset{+}{N}$.OAc) cm^{-1}, τ ($CF_3.CO_2H$) 1.50-2.36 (9H, m, ArH) and 7.76 (3H, s, $\overset{+}{N}$.OAc).

(g) 4-N-Acetoxy-6-chloro-1,2-dihydro-2-oxo-3-phenylquinoxalinium perchlorate (105g) was prepared from the N-oxide (104g)[41] as a yellow crystalline solid (ca. 0.75 g) (ca. 91%), ν_{max} 1830 (cyclic $\overset{+}{N}$.OAc) cm^{-1}, τ ($CF_3.CO_2H$) 1.61 (1H, d, J_{meta} 2.0 Hz, H-5), 1.94-2.38 (7H, m, ArH) and 7.76 (3H, s, $\overset{+}{N}$.OAc).

(h) 4-N-Acetoxy-1,2-dihydro-6-methyl-2-oxo-3-phenylquinoxalinium perchlorate (105h) was prepared from the N-oxide (104h)[14] as a yellow crystalline solid (ca. 0.68 g) (ca. 86%), ν_{max} 1840 (cyclic $\overset{+}{N}$.OAc), τ ($CF_3.CO_2H$) 1.70-2.46 (8H, m, ArH), 7.37 (3H, s, CH_3) and

7.77 (3H, s, $\overset{+}{N}$.OAc).

(i) 4-N-Acetoxy-1,2-dihydro-6-methoxy-7-oxo-3-phenylquinoxalinium perchlorate (105i) was prepared from the N-oxide (104i)[14] (0.54g, 0.002 mol) as a yellow crystalline solid (ca. 0.80 g) (ca. 98%), ν_{max} 1830 (cyclic $\overset{+}{N}$.OAc), τ ($CF_3.CO_2H$) 2.00-2.46 (8H, m, ArH), 5.96 (3H, s, O.CH_3) and 7.76 (3H, s, N.OAc), $^m/_e$ 310, M^+ (cation) 311.

(j) 4-N-Acetoxy-1,2-dihydro-6,7-dimethyl-2-oxo-3-phenylquinoxalinium perchlorate (105j) was prepared from the N-oxide (104j)[14] as a yellow crystalline solid (ca. 0.64 g) (ca. 80%), ν_{max} 1830 (cyclic $\overset{+}{N}$.OAc) cm^{-1}, τ ($CF_3.CO_2H$) 1.80 (1H, s, H-5), 2.02-2.46 (6H, m, ArH), 7.42 (3H, s, CH_3), 7.45 (3H, s, CH_3) and 7.76 (3H, s, $\overset{+}{N}$.OAc).

(k) 1,4,N,N-Diacetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium perchlorate (107a) was prepared from the N-oxide (106a)[14] as a yellow crystalline solid (ca.0.80g) ca. 92%), ν_{max} 1840 (cyclic $\overset{+}{N}$.OAc) and 1810 (cyclic N.OAc) cm^{-1}.

The acetic acid - acetic anhydride mother liquors from the preparation of the perchlorate (107a) were diluted with ether (100 ml) and washed with saturated aqueous sodium hydrogen carbonate. The ether layer was evaporated to give a brown intractable gum (0.05g).

Attempts to obtain the ^{1}H n.m.r. spectrum of the perchlorate (107a) in trifluoroacetic acid were unsuccessful due to its instability.

(l) 1,4,N,N-Diacetoxy-1,2-dihydro-7-methyl-2-oxo-3-phenylquinoxalinium perchlorate (107b) was prepared from the N-oxide (106b)[39] as a yellow crystalline solid (ca. 0.31g) (ca. 34%), ν_{max} 1845 (cyclic $\overset{+}{N}$.OAc) and 1810 (cyclic N.OAc) cm^{-1}, τ ($CF_3.CO_2H$) 1.60-2.40 (8H, m, ArH), 7.28 (3H, s, CH_3) and 7.78 (6H, s, N.OAc and $\overset{+}{N}$.OAc).

The acetic acid - acetic anhydride mother liquors from the preparation of the perchlorate (107b) were diluted with the ether

used to wash the perchlorate (107b) and washed with water (10 ml). The ether layer was separated, washed with saturated aqueous sodium hydrogen carbonate (10 ml), water (10 ml), and evaporated to give 1,6-diacetoxy-7-methyl-3-phenylquinoxalin-2(1H)-one (111a) as cream coloured needles (0.22 g) (31%) m.p. 191° (from ethanol-glacial acetic acid), ν_{max} 1800 (cyclic N.OAc), 1740 (C.OAc) and 1680 (CO) cm^{-1}, τ ($CDCl_3$) 1.60-1.74 (2H, m, ArH), 2.36 (1H, s, H-5), 2.42 (3H, m, ArH), 2.92 (1H, s, H-8), 7.50 (3H, s, CH_3), 7.65 (3H, s, OAc) and 7.70 (3H, s, OAc).

Found: C, 64.5; H, 4.5; N, 7.9%; M^+ 352

$C_{19}H_{16}N_2O_5$ requires: C, 64.8; H, 4.6; N, 7.9%; M 352

The aqueous washings were acidified with 5M aqueous sulphuric acid but gave no solid material.

(m) 7-Chloro-1,4,N,N-diacetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium perchlorate (107c)

In the case of the N-oxide (106c),[14] the quinoxalinium perchlorate (107c) did not crystallise from the dark red solution which was obtained and the reaction mixture was therefore added dropwise with stirring to dry ice-cold ether (200 ml) giving a gummy yellow solid (A).

The supernatant liquor was decanted off, washed with water (10 ml) and saturated aqueous sodium hydrogen carbonate solution (10 ml) and evaporated to yield 7-chloro-1,6-diacetoxy-3-phenylquinoxalin-2(1H)-one (111b) as cream coloured prisms (0.12 g) (16%), m.p. 206° (from ethanol-glacial acetic acid), ν_{max} 1795 (cyclic N.OAc), 1770 (C.OAc) and 1690 (CO) cm^{-1}, τ ($CDCl_3$) 1.66-1.80 (2H, m, ArH), 2.48-2.64 (3H, m, ArH), 2.80 (1H, s, H-5), 2.92 (1H, s, H-8), 7.54 (3H, s, OAc) and 7.60 (3H, s, OAc).

Found: C, 57.8; H, 3.5; N, 7.5%; M^+ 372 (374)

$C_{18}H_{13}ClN_2O_5$ requires: C, 58.0; H, 3.5; N, 7.5%; M 372.5

The aqueous washings were acidified with 5M aqueous sulphuric acid but yielded no further material.

The gummy yellow solid (A) was dissolved in ethanol (2.5 ml) and the solution was heated under reflux on a steam bath for 30 min. The reaction mixture was allowed to cool, diluted with water (6.0 ml) and extracted with chloroform. The extract was washed with saturated aqueous sodium hydrogen carbonate (5.0 ml), dried and evaporated to give a yellow solid (0.22 g) m.p. 80-175°, ν_{max} 3400-2400 br (OH), 1800 w (N.OAc) and 1640 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.80-2.60 (9 units, m, ArH), 5.42-5.82 (2 units, m, CH_2) and 8.20-8.80 (3 units, m, CH_3). The ^1H n.m.r. spectrum showed that the solid was a mixture and attempts to crystallise the solid were unsuccessful.

(n) 4-N-Acetoxy-2-cyano-3-phenylquinoxalinium perchlorate 1-N-oxide (113) or 1-N-acetoxy-2-cyano-3-phenylquinoxalinium perchlorate 4-N-oxide (114) was prepared from 2-cyano-3-phenylquinoxaline 1,4-di-N-oxide (112)[14] (0.53 g, 0.002 mol) as a yellow crystalline solid (ca. 0.80g) (ca. 98%), ν_{max} 1820 (cyclic $\overset{+}{N}$.OAc) cm^{-1}, τ ($CF_3.CO_2H$) 1.22-2.30 (4H, m, ArH) and 7.74 (3H, s, N.OAc).

On treatment with hot ethanol, the perchlorate (113) or (114) was converted to the di-N-oxide (112) identical (i.r. spectrum) with an authentic sample.

Investigation of the Effect of Acetonitrile on the Quinoxalinium Perchlorate (105b)

A solution of the perchlorate (105b) prepared from 1.0 g, 0.0036 mol of the N-oxide (104b) in redistilled acetonitrile (30 ml) was stirred at room temperature for 10 min. The reaction mixture

was concentrated, treated with water (10 ml) and extracted with chloroform. The chloroform extract was washed with 5M aqueous sodium hydroxide solution (5.0 ml) and evaporated to yield a brown gum (0.49 g) which was shown by t.l.c. (chloroform) comparison with authentic samples to be a mixture of the N-oxide (104b) and the deoxygenated compound (110b). The gum was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave the deoxygenated compound (110b) (0.13 g) (13%) m.p. 160° (lit.[14] 162°) identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene gave the N-oxide (104b) (0.28 g) (36%), m.p. 188° (lit.[14] 189°), identical (i.r. spectrum) with an authentic sample.[14]

The alkaline washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform to give the 7-hydroxy compound (115g) (0.35 g) (35%) m.p. 260° (from glacial acetic acid), identical (i.r. spectrum) with a sample obtained before.

3.2 The Reactions of Quinoxalinium Perchlorates with Anions

I. General Method for Reactions in Glacial Acetic Acid

The quinoxalinium perchlorate (105) [prepared from 0.002 mol of the corresponding N-oxide (104)] was added in portions to a solution of the dry inorganic salt (0.008 mol) in glacial acetic acid (10 ml).

The perchlorate dissolved giving a yellow solution which was stirred at room temperature for 0.5 h. Any solid (A) was collected, washed with water (10 ml) and dried *in vacuo*. The reaction mixture was diluted with water (20 ml) and any further solid (B) was collected, washed with water and dried *in vacuo*.

The aqueous acetic acid mother liquors were neutralised by the

addition of solid sodium hydrogen carbonate and extracted with chloroform to give more material (C).

II General Method for Reactions in Diethyl Ether

A suspension of the quinoxalinium perchlorate (105) [prepared from 0.002 mol of the corresponding N-oxide (104)] was stirred vigorously in sodium dried ether (100 ml) at room temperature and the dry, finely powdered inorganic salt (0.008 mol) was added.

The reaction mixture was stirred vigorously at room temperature for 0.5-3.0 h and then ethanol (25 ml) was added in order to decompose any unreacted quinoxalinium perchlorate.

The pale yellow solution which resulted was stirred at room temperature for 0.5 h, filtered to remove any solid, concentrated under reduced pressure almost to dryness and treated with water (10 ml) to give solids or gums which were purified as described under the individual reactions.

1. Reactions of Quinoxalinium Perchlorates with Sodium Acetate

(a) 4-N-Acetoxy-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalinium perchlorate (105a) reacted with fused sodium acetate as described in the general method I to give a pale yellow solution which on dilution with water (20 ml) and extraction with chloroform (C) gave a brown gum. Trituration of the gum with ether gave 7-acetoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (115a) (0.35 g) (60%), m.p. 126° (from ethanol) (lit.[38] 126°) identical (i.r. spectrum) with an authentic sample.[14]

(b) 4-N-Acetoxy-6-chloro-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalinium Perchlorate (105b)

(i) The quinoxalinium perchlorate (105b) reacted with fused sodium acetate as described in the general method I to give a pale yellow solution. Dilution with water (20 ml) and extraction with

chloroform (C) gave a gummy yellow solid which on trituration with ether gave 7-acetoxy-6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (115b) (0.35 g) (53%), m.p. 170° (from ethanol) (lit.[14] 171°) identical (i.r. spectrum) with an authentic sample.[14]

The ether mother liquors were evaporated to give a brown solid (0.05 g) which was crystallised from ethanol to give a further crop of the 7-acetoxy compound (115b) (0.02 g) m.p. 170° identical (i.r. spectrum) with the first crop.

(ii) The perchlorate (105b) was stirred in dry ether with fused sodium acetate for 0.5h as described in the general method II to give a yellow solid which was crystallised from ethanol to afford the 7-acetoxy compound (115b) (0.44 g) (67%), m.p. 170° (lit.[14] 171°) identical (i.r. spectrum) with an authentic sample.[14]

(c) 4-N-Acetoxy-1,2-dihydro-2-oxo-1,6,7-trimethyl-3-phenyl quinoxalinium perchlorate (105e) reacted with fused sodium acetate as described in the general method I to give a yellow solid (A) (0.11 g) m.p. 80-100°, ν_{max} 1730 (C.OAc) cm^{-1}. A further crop of the solid was obtained by extraction of the acetic acid mother liquors with chloroform (C) (0.4 g). The solids were shown by t.l.c. (chloroform) to be mixtures of the same two components and they were therefore combined and chromatographed on alumina.

Elution with toluene gave small amounts of unidentified yellow and brown gums (total 0.14 g).

Elution with ether gave 1,6-dimethyl-7-hydroxymethyl-3-phenyl quinoxalin-2(1H)-one (115d) (0.28 g) (51%), m.p. 132° (from ethanol) (lit.[14] 133°), ν_{max} 3400 br (OH) and 1635 (CO) cm^{-1}, τ ($CDCl_3$) 1.62-1.80 (2H, m, ArH), 2.39 (1H, s, H-5), 2.46-2.64(3H, m, ArH), 2.70 (1H, s, H-8), 5.29 (2H, s, CH_2), 6.36 (3H, s, $N.CH_3$) and

7.73 (3H, s, CH_3), identical (i.r. spectrum) with an authentic sample.[14]

(d) 4-N-Acetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium perchlorate (105f)

(i) The quinoxalinium perchlorate (105f) reacted with fused sodium acetate as described in the general method I to give a yellow solid (A) which was washed with glacial acetic acid (1.0 ml), water, and dried. The yellow solid (0.25 g) crystallised unchanged (i.r. spectrum) from glacial acetic acid, m.p. 210-218°, ν_{max} 1755 (C.OAc) and 1660 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.47 (1 unit, dd, J_{ortho} 9.0 Hz, J_{meta} 2.0 Hz, ArH), 1.66-1.86 (3 units, m, ArH), 2.00-2.60 (12 units, m, ArH) and 7.51 (3 units, s, C.OAc); m/e 280 [7-acetoxy-3-phenylquinoxalin-2(1H)-one (115e)] and 238 [N-oxide (104f)].

Further attempts to resolve the mixture by crystallisation were unsuccessful.

The acetic acid mother liquors were diluted with water (20 ml) and extracted with chloroform to give a yellow solid (C) (0.21 g) which was crystallised from glacial acetic acid to give the N-oxide (104f) (0.15 g) (31%), m.p. 285° (lit.[40] 285°) identical (i.r. spectrum) with an authentic sample.[14]

(ii) A suspension of the perchlorate (105f) [prepared from 1.90 g, 0.008 mol of the N-oxide (104f)] was stirred in dry ether (200 ml) with fused sodium acetate (3.2 g, 0.032 mol) for 3 h. Ethanol (50 ml) was added, the reaction mixture was stirred for a further 1h and filtered to remove the insoluble sodium acetate.

The filtrate was concentrated, treated with water (10 ml) and extracted with chloroform to give a yellow solid (1.5 g), m.p.

150-200° with an ester like smell. The solid was washed with light petroleum (50 ml) to give a yellow solid (1.3 g), ν_{max} 1720 (CO) and 1650 (CO) cm^{-1}, which was shown by t.l.c. (chloroform) to be a two component mixture and was chromatographed on silica.

Elution with toluene-ether (9:1) gave a cream coloured solid (0.33 g) m.p. 200-250°, ν_{max} 1725 (CO) and 1690 (CO) cm^{-1}, $\tau(CF_3.CO_2H)$ 1.78-2.92 (14 units, m, ArH), 5.69 (2 units, q, J 7.0 Hz, CH_2) and 8.45 (3 units, t, J 7.0 Hz, CH_3), consistent with a mixture of 7-ethoxy-3-phenylquinoxalin-2(1H)-one (1261) and another component containing only aromatic protons.

Elution with toluene-ether (2:1) gave 7-ethoxy-3-phenylquinoxalin-2(1H)-one (1261) (0.40 g) (19%), m.p. 223° (from glacial acetic acid) identical (i.r. spectrum) with a sample obtained previously.

The light petroleum which was used to wash the yellow solid was evaporated to yield ethyl benzoate (0.09 g), ν_{max} (liquid film) 1730 (CO) cm^{-1}, identical (i.r. spectrum) with an authentic sample.

(e) 4-N-Acetoxy-1,2-dihydro-6,7-dimethyl-2-oxo-3-phenylquinoxalinium Perchlorate (105j)

A suspension of the perchlorate (105j) was stirred vigorously in dry ether (100 ml) with finely powdered fused sodium acetate (0.65 g, 0.008 mol) for 1.5 h. The reaction mixture was filtered to give a yellow solid (2.6 g) the i.r. spectrum of which was identical with that of the starting quinoxalinium perchlorate (105j). The yellow solid was dissolved in ethanol (20 ml) and the solution was heated under reflux on a boiling water bath for 15 min. The reaction mixture was allowed to cool and a yellow solid was obtained

which was collected to yield the N-oxide (104j) (0.06 g) (11%), m.p. 280° (lit.[14] 286°) identical (i.r. spectrum) with an authentic sample.[14] The ethanol mother liquors were concentrated, treated with water (10 ml) and extracted with chloroform to give a brown gum (0.4 g) which failed to produce any solid on trituration with organic solvents.

The ether filtrate was washed with water (10 ml) and evaporated to give a solid (0.07 g) which on crystallisation from ethanol-glacial acetic acid gave a further crop of the N-oxide (104j) (0.02 g), m.p. 285° identical (i.r. spectrum) with an authentic sample. The mother liquors from the crystallisation were evaporated to give a brown intractable residue (0.04 g).

2. Reactions of Quinoxalinium Perchlorates with Lithium Chloride

(a) 4-N-Acetoxy-6-chloro-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalinium Perchlorate (105b)

(i) A suspension of the perchlorate (105b) in dry ether (100 ml) was stirred with lithium chloride (0.33 g, 0.008 mol) for 0.5 h. The reaction mixture was worked up as described in the general method II to give a gummy yellow solid which was extracted into chloroform and washed with 5M aqueous sodium hydroxide solution. The extract was evaporated to yield a yellow solid (0.3 g) which was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave 6,7-dichloro-1-methyl-3-phenylquinoxalin-2(1H)-one (115j) (0.21 g) (38%), m.p. 170° (from ethanol) (lit.[14] 171°) identical (i.r. and ^{1}H n.m.r. spectra) with an authentic sample.[14]

The alkaline washings were acidified with 5M aqueous hydrochloric acid and extracted with chloroform to give the 7-hydroxy compound (115g) (0.03 g) (6%), m.p. 255°, identical (i.r. spectrum)

with a sample prepared previously.

(ii) The quinoxalinium perchlorate (105b) reacted with lithium chloride as described in the general method I to give a yellow solution which on dilution with water (20 ml) gave a yellow solid (B) (0.51 g). The solid was shown by t.l.c. (chloroform) to be a two component mixture and was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave the dichloro compound (115j) (0.20 g) (33%), m.p. 171° (from ethanol) (lit.[14] 171°) identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene gave the N-oxide (104b) (0.22 g) (38%), m.p. 189° (from ethanol) (lit.[14] 189°) identical (i.r. spectrum) with an authentic sample.

(b) 4-N-Acetoxy-1,2-dihydro-1,6-dimethyl-2-oxo-3-phenylquinoxalinium perchlorate (105c) reacted with lithium chloride as described in the general method I to give a yellow solution which on dilution with water (15 ml) gave a yellow solid (B) (0.42 g). The solid was shown by t.l.c. (chloroform) to be a two component mixture and a further crop of the solid (C) (0.03 g) was obtained by extraction of the aqueous acetic acid mother liquors with chloroform. The solids were combined and chromatographed on alumina.

Elution with light petroleum-toluene (2:1) afforded 7-chloro-1,6-dimethyl-3-phenylquinoxalin-2(1H)-one (115k) (0.16 g) (38%), m.p. 160° (from ethanol) (lit.[14] 162°) identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene gave the N-oxide (104c) (0.26 g) (49%), m.p. 236° (from ethanol) (lit.[14] 238°) identical (i.r. spectrum) with an authentic sample.

(c) 4-N-Acetoxy-1,2-dihydro-2-oxo-1,6,7-trimethyl-3-phenylquinoxalinium perchlorate (105e) reacted with lithium chloride as described in the general method I to give a yellow solution which on dilution with water (10 ml) gave a yellow solid (B) (0.37 g). The solid was shown by t.l.c. (chloroform) to be a two component mixture and a further crop of the solid (C) (0.07 g) was obtained by extraction of the aqueous acetic acid mother liquors with chloroform. The solids were combined and chromatographed on alumina.

Elution with light petroleum-toluene (2:1) gave 8-chloro-3-phenyl-1,6,7-trimethylquinoxalin-2(1H)-one (123) (0.07 g) (13%), m.p. 160° (from ethanol) (lit.[14] 157°), ν_{max} 1650 (CO) cm^{-1}, $\tau(CDCl_3)$ 1.64-1.80 (2H, m, ArH), 2.42 (1H, s, H-5), 2.48-2.62 (3H, m, ArH), 6.03 (3H, s, $N.CH_3$), 7.56 (3H, s, CH_3) and 7.62 (3H, s, CH_3), identical (i.r. and ^1H n.m.r. spectra) with an authentic sample.[14]

Elution with toluene gave 5-chloro-3-phenyl-1,6,7-trimethylquinoxalin-2(1H)-one (124) as pale yellow needles (0.06 g) (10%), m.p. 196° (from ethanol), ν_{max} 1650-1660 (CO) cm^{-1}, τ ($CDCl_3$) 1.48-1.64 (2H, m, ArH), 2.50-2.66 (3H, m, ArH), 3.10 (1H, s, H-8), 6.36 (3H, s, $N.CH_3$) and 7.62 (6H, s, CH_3).

Found: C, 68.5; H, 5.1; N, 9.3%: M^+ 298 (300)

$C_{17}H_{15}ClN_2O$ requires: C, 68.3; H, 5.0; N, 9.4%: M 298.5

Further elution with toluene gave the N-oxide (104e) (0.29 g) (52%), m.p. 200° (from ethanol) (lit.[14] 200°) identical (i.r. spectrum) with an authentic sample.[14]

(d) 4-N-Acetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium perchlorate (105f) reacted with lithium chloride as described in the general method I to give a yellow solid (A) (0.24 g) a further crop (0.20 g)

of which was obtained by dilution of the acetic acid mother liquors (B) with water (20 ml). The combined solids were crystallised from glacial acetic acid to afford the N-oxide (104f) (0.35 g) (83%), m.p. 284° (lit.[40] 286°) identical (i.r. spectrum) with an authentic sample.

(e) 1,4-N,N-Diacetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium perchlorate (107a) reacted with lithium chloride as described in the general method I to give a pale yellow solution which was diluted (B) with water (20 ml) to give 1-N-acetoxy-3-phenylquinoxalin-2(1H)-one 4-N-oxide (125) (0.37 g) (62%), m.p. 173° (lit.[14] 174°) identical (i.r. spectrum) with an authentic sample.[14]

3. Reactions of the Quinoxalinium Perchlorate (105b) with Lithium Bromide

(i) The quinoxalinium perchlorate (105b) reacted with lithium bromide as described in the general method I to give a yellow solid (A) more of which was obtained by dilution of the acetic acid mother liquors with water (10 ml) and extraction with chloroform (C). The solids were combined and crystallised from ethanol-glacial acetic acid to yield the N-oxide (104b) (0.54 g) (95%), m.p. 187° (lit.[14] 189°) identical (i.r. spectrum) with an authentic sample.

(ii) A suspension of the quinoxalinium perchlorate (105b) in dry ether (100 ml) was stirred with lithium bromide (0.70 g, 0.008 mol) at room temperature for 1.5 h. Water (5.0 ml) was added and the mixture was stirred for 5 min giving a pale yellow solution which was concentrated and extracted with chloroform. The extract was washed with 5 M aqueous sodium hydroxide solution (2 x 10 ml) and evaporated to give the N-oxide (104b) (0.42 g) (73%), m.p. 187° (from ethanol) (lit.[14] 189°) identical (i.r. and ^{1}H n.m.r. spectra) with an authentic sample.

The alkaline washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform to afford 6-chloro-7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (115g) (0.05 g) (9%), m.p. 255° (from glacial acetic acid) identical (i.r. spectrum) with a sample obtained previously.

4. Reactions of the Quinoxalinium Perchlorate (105b) with Sodium Thiocyanate

(i) The quinoxalinium perchlorate (105b) reacted with sodium thiocyanate as described in the general method I to give a yellow solid (A) which on washing with water (5.0 ml) afforded 6-chloro-1-methyl-3-phenyl-7-thiocyanatoquinoxalin-2(1H)-one (115i) as yellow plates (0.25 g) (38%), m.p. 176° (from ethanol), ν_{max} 2200 (·N=C=S), 1660 (CO) cm^{-1}, τ ($CDCl_3$) 1.63-1.77 (2H, m, ArH), 2.04 (1H, s, H-5), 2.44 (1H, s, H-8), 2.46-2.58 (3H, m, ArH) and 6.26 (3H, s, $N.CH_3$).

Found: C, 58.3; H, 3.0; N, 12.8%: M^+ 327 (329)

$C_{16}H_{16}ClN_3OS$ requires: C, 58.6; H, 3.0; N, 12.8%: M 327.5

The acetic acid mother liquors were diluted with water (20 ml), neutralised by the addition of solid sodium hydrogen carbonate and extracted with chloroform to give a yellow solid (C) (0.48 g) which was shown by t.l.c. (chloroform) to be a four component mixture and was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) afforded 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (110b) (0.11 g) (20%), m.p. 161° (from ethanol) (lit.[14] 162°) identical (i.r. spectrum) with an authentic sample.

Further elution with light petroleum-toluene (1:1) gave the 7-thiocyanato compound (115i) (0.025 g) (4%) m.p. 168°, identical

(i.r. spectrum) with the sample obtained previously.

Elution with toluene gave the N-oxide (104b) (0.20 g) (35%), m.p. 189° (from ethanol-glacial acetic acid) (lit.[14] 189°) identical (i.r. spectrum) with an authentic sample.

Elution with ether and chloroform gave an intractable brown gum (0.025 g) and an unidentified yellow solid (0.04g).

(ii) A suspension of the quinoxalinium perchlorate (105b) [prepared from 1.0 g, 0.0035 mol of the N-oxide (104b)] was stirred in dry ether (200 ml) with sodium thiocyanate (1.3 g, 0.016 mol) for 1 h and than filtered to give a yellow solid which was triturated with ethanol (20 ml) and then collected by filtration and washed with water (5.0 ml) to give the 7-thiocyanato compound (115i) (0.25 g) (22%), m.p. 176° (from ethanol) identical with a sample obtained previously.

The ethanol mother liquors were evaporated and treated with water (10 ml) to give a gummy yellow solid which was crystallised from ethanol to afford 6-chloro-7-ethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126c) (0.13 g) (12%), m.p. 180° identical (i.r. spectrum) with a sample prepared previously.

The ether mother liquors were washed with 5M aqueous sodium hydroxide (10 ml) and evaporated to give a gummy yellow solid (0.14 g) which on crystallisation from ethanol gave a further crop of the thiocyanato compound (115i) (0.07 g) (6%), m.p. 170° identical (i.r. spectrum) with a sample prepared previously.

The alkaline washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform to give the 7-hydroxy compound (115g), (0.03 g) (6%), m.p. 260° identical (i.r. spectrum) with a sample obtained before.

5. Reaction of the Quinoxalinium Perchlorate (105b) with Sodium Amide

A suspension of the quinoxalinium perchlorate (105b) in dry ether (100 ml) was stirred with freshly prepared sodium amide (0.27 g, 0.008 mol) for 0.5 h and then filtered to remove some insoluble solid. The ether was evaporated to give a red gum (0.37 g) which was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (110b) (0.06 g) (12%), m.p. 161° (from ethanol) (lit.[14] 162°) identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene-ether (20:1) gave an unidentified yellow solid (0.02 g) m.p. 140-170°, ν_{max} 1660 (CO) cm^{-1}.

Further elution with toluene-ether (20:1) gave an unidentified orange solid (0.03 g) m.p. 135-180°, ν_{max} 1660 (CO) cm^{-1}. Elution with toluene-ether (1:2) gave a brown intractable gum (0.15 g).

The solid which was insoluble in the original ethereal reaction mixture was dissolved in water (5 ml). Acidification of the solutions with 5M aqueous sulphuric acid and extraction with chloroform yielded no further material.

6. Reactions of Quinoxalinium Perchlorates with Metal Cyanides

(a) 4-N-Acetoxy-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalinium Perchlorate (105a)

(i) The quinoxalinium perchlorate (105a) [prepared from 0.50 g, 0.002 mol of the N-oxide (104a)] was treated with 5M aqueous potassium cyanide solution (10 ml) giving a fluorescent solution which was heated under reflux on a steam bath for 0.5 h, diluted with water (10 ml) and filtered to give 7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (115h) (0.22 g) (44%), m.p. 300° (from glacial

acetic acid) (lit.[14,38] 300°) identical (i.r. spectrum) with an authentic sample.[14]

The filtrate was acidified with 5M aqueous sulphuric acid and extracted with chloroform. Evaporation of the extract gave no material. The acidic solution was adjusted to pH 7 by the addition of solid sodium hydrogen carbonate and extracted with chloroform but afforded no further material.

(ii) The quinoxalinium perchlorate (105a) [prepared from 0.50 g, 0.002 mol of the N-oxide (104a)] was dissolved in dimethylformamide (20 ml) at room temperature and the solution was added to a hot solution of sodium cyanide (0.39 g, 0.008 mol) in dimethylformamide (100 ml). The mixture was allowed to stand at room temperature for 0.5 h and was then diluted with water (200 ml) and extracted with chloroform to give the 7-hydroxy compound (115h) (0.35 g) (70%), m.p. 300° (from glacial acetic acid) (lit.[14,38] 300°) identical (i.r. spectrum) with an authentic sample.[14]

(b) 4-N-Acetoxy-6-chloro-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalinium Perchlorate (105b)

(i) A suspension of the perchlorate (105b) in dry ether (100 ml) was treated with sodium cyanide (0.40 g, 0.008 mol) as described in the general method II to give a yellow gummy solid (0.1 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

The aqueous washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform to give the 6-chloro-7-hydroxy compound (115g) (0.3 g) (60%), m.p. 255° (from glacial acetic acid) identical with a sample obtained previously.

(ii) A suspension of the perchlorate (105b) in dry ether (100 ml) was treated with silver cyanide (1.1 g, 0.008 mol), as described in the general method II to give a gummy solid which was extracted

into chloroform and washed with 5M aqueous sodium hydroxide solution. The extract was evaporated to give 6-chloro-7-ethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126c) (0.3 g) (53%), m.p. 181° (from ethanol) identical (i.r. spectrum) with a sample prepared previously.

The alkaline washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform to give the 6-chloro-7-hydroxy compound (115g) (0.1 g) (20%), m.p. 255° (from glacial acetic acid), identical with a sample obtained before.

7. Reactions of the Quinoxalinium Perchlorate (105b) with Sodium Azide.

(i) A suspension of the perchlorate (105b) in dry ether (100 ml) was treated with sodium azide (0.52 g, 0.008 mol) as described in the general method II to give a yellow solid which was dissolved in chloroform and washed with 5M aqueous sodium hydroxide solution (2 x 10 ml). The chloroform extract gave a yellow solid (0.23 g) which was shown by t.l.c. (chloroform) to be a mixture of at least two components. The mixture was chromatographed on alumina. Elution with light petroleum-toluene (1:2) gave 7-azido-6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (115f) (0.05 g) (9%), m.p. 160°, ν_{max} 2175 (N_3) and 1660 (CO) cm^{-1}, τ ($CDCl_3$) 1.64-1.78 (2H, m, ArH), 2.08 (1H, s, H-5), 2.42-2.62 (3H, m, ArH), 3.05 (1H, s, H-8) and 6.28 (3H, s, $N.CH_3$).

Further elution with light petroleum-toluene (1:2) gave 6-chloro-7-ethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126c) (0.16 g) (28%), m.p. 181° (from ethanol) identical (i.r. spectrum) with a sample obtained previously.

The alkaline washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform to give the 6-chloro-7-hydroxy

compound (115g) (0.17 g) (35%), m.p. 256°, identical (i.r. spectrum) with a sample obtained before.

(ii) The reaction (i) was repeated with the modification that the reaction mixture was stirred at room temperature for 3 h. The gummy solid which was obtained (0.37 g) was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave the 7-azido compound (115f) (0.1 g) (18%), m.p. 160°, identical (i.r. spectrum) with the sample obtained in the previous reaction. The solid deteriorated on standing.

Elution with toluene gave the 7-ethoxy compound (126c) (0.16 g) (28%), m.p. 181° (from ethanol) identical (i.r. spectrum) with a sample obtained before.

Further elution with toluene gave the N-oxide (104b) (0.04 g) (8%), m.p. 189° (from ethanol) (lit.[14] 189°) identical (i.r. spectrum) with an authentic sample.[14]

The alkaline washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform to give the 7-hydroxy compound (115g) (0.1 g) (20%), m.p. 254° (from glacial acetic acid) identical (i.r. spectrum) with a sample obtained before.

3.3 Reactions of Quinoxalinium Perchlorates with Alkali and Water

(i) The quinoxalinium perchlorate (105a) [prepared from 0.5 g, 0.002 mol of the N-oxide (104a)] was treated with 5M aqueous sodium hydroxide (25 ml). The mixture was heated under reflux for 1 min and then hot filtered. The insoluble material was washed with water and dried to yield the 7-hydroxy compound (115h) (0.1 g) (20%), m.p. 280-300° (lit.[14,38] 300°), identical (i.r. spectrum) with an authentic sample.[14]

The aqueous sodium hydroxide was acidified with 5M aqueous

sulphuric acid and the yellow precipitate was collected, washed with water and sucked dry to give the 7-hydroxy compound (115h) (0.15 g) (30%), m.p. 295-307°, identical (i.r. spectrum) with an authentic sample.[14]

(ii) The quinoxalinium perchlorate (105b) [prepared from 0.57 g, 0.002 mol of the N-oxide (104b)] was treated with water and the yellow suspension was stirred at room temperature for 1 h. The solid was collected, washed with water (10 ml) and dried in vacuo to yield 6-chloro-7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (115g) as yellow prisms (0.54 g) (95%), m.p. 261° (from glacial acetic acid), ν_{max} 3300-3200 br (OH) and 1660 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.76 (1H, s, H-5), 1.80-2.33 (5H, m, ArH), 2.54 (1H, s, ArH) and 5.98 (3H, s, $N.CH_3$).

Found: C, 62.7; H, 3.8; N, 9.9%: M^+ 286 (288)

$C_{15}H_{11}ClN_2O_2$ requires: C, 62.8; H, 3.8; N, 9.8%: M 286.5

(iii) The quinoxalinium perchlorate (107a) [prepared from 0.50 g, 0.002 mol of the N-oxide (106a)] was stirred in water (5.0 ml) at room temperature for 1 h. A brown solid was obtained (0.36 g) m.p. 100-107° which was shown by t.l.c. (chloroform) to be a multicomponent mixture. Attempts to purify the solid by crystallisation were unsuccessful.

(iv) The quinoxalinium perchlorate (105f) [prepared from 0.47 g, 0.002 mol of the N-oxide (104f)] reacted with water (5.0 ml) as described in the previous experiment to give a brown solid (0.45 g) m.p. 200-250°, ν_{max} 3400-3100 br (OH) and 1660 (CO) cm^{-1}. Attempted crystallisation of the solid from a variety of solvents gave intractable gums.

3.4 The Reactions of N-Acetoxyquinoxalinium Perchlorates with Alcohols

General Method

The freshly prepared N-acetoxyquinoxalinium perchlorate (105) or (107) [prepared from 0.002 mol of the corresponding N-oxide (104) or (106)] was added to the alcohol (2.5-10 ml) at room temperature. A vigorous reaction took place and a yellow crystalline solid was obtained. The reaction mixture was heated on a boiling water bath for 0.5 h and the volume of alcohol was increased (2.5-160 ml) until all the solid was in solution. On cooling, the yellow crystalline solid was collected by filtration, washed with a little alcohol, followed by water and dried in vacuo to yield the product.

The mother liquors were worked up as described in the individual reactions.

The quantities described in this general method were used in experiements 3.4 (a)-(w).

(a) 7-Ethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126a)

The quinoxalinium perchlorate (105a) reacted with ethanol (10 ml) to give 7-ethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126a) as yellow prisms (0.40 g) (71%), m.p. 111° (from ethanol), ν_{max} 1650 (CO) cm^{-1}, τ ($CDCl_3$) 1.66-1.85 (2H, m, ArH), 2.21 (1H, d, J_{ortho} 9.0 Hz, H-5), 2.50-2.68 (3H, m, ArH), 3.13 (1H, dd, J_{ortho} 9.0 Hz, J_{meta} 2.5 Hz, H-6), 3.34 (1H, d, J_{meta} 2.5 Hz, H-8), 5.88 (2H, q, J 7.0 Hz, CH_2), 6.34 (3H, s, $N.CH_3$) and 8.54 (3H, t, J 7.0 Hz, CH_3).

Found: C, 72.5; H, 5.5; N, 9.9%: M^+ 280

$C_{17}H_{16}N_2O_2$ requires: C, 72.8; H, 5.7; N, 10.0%: M 280

The ethanol mother liquors were concentrated under reduced pressure, treated with saturated aqueous sodium hydrogen carbonate (10 ml) and extracted with chloroform to give a brown gum (0.12 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(b) 7-Methoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (125b)

The quinoxalinium perchlorate (105a) was heated under reflux in methanol (30 ml) for 0.5 h. The reaction mixture was concentrated, treated with water (10 ml) and extracted with chloroform to give a yellow solid (0.20 g) which was crystallised from light petroleum-benzene to give the 7-hydroxy compound (115h) (0.03 g) (6%), m.p. 290° (lit.[14,38] 300°) identical (i.r. spectrum) with an authentic sample.[14]

The mother liquors were evaporated to afford 7-methoxy-1-methyl--3-phenylquinoxalin-2(1H)-one (126b) (0.12 g) (22%) m.p. 95° (lit.[14] 96°) identical (i.r. spectrum) with an authentic sample.[14]

(c) 6-Chloro-7-ethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126c)

The quinoxalinium perchlorate (105b) reacted with ethanol (25 ml) to give 6-chloro-7-ethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126c) as pale yellow prisms (0.36 g) (57%), m.p. 181° (from ethanol-glacial acetic acid), ν_{max} 1660 (CO) cm^{-1}, τ ($CDCl_3$) 1.62-1.86 (2H, m, ArH), 2.19 (1H, s, H-5), 2.48-2.68 (3H, m, ArH), 3.45 (1H, s, H-8), 5.87 (2H, q, J 7.0 Hz, CH_2), 6.39 (3H, s, $N.CH_3$) and 8.49 (3H, t, J 7.0 Hz, CH_3).

Found: C, 64.8; H, 4.7; N, 9.4%: M^+ 314 (316)

$C_{17}H_{15}ClN_2O_2$ requires: C, 64.8; H, 4.8; N, 8.9%: M 314.5

The ethanol mother liquors were concentrated and treated with water (10 ml) to give a yellow solid which was crystallised from ethanol to yield a further crop of the ethoxy compound (126c) (0.05 g)

m.p. 179° identical (i.r. spectrum) with the first crop.

(d) 6-Chloro-7-methoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126d)

The quinoxalinium perchlorate (105b) reacted with methanol (30 ml) to give 6-chloro-7-methoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126d) as pale yellow needles (0.33 g) (63%), m.p. 188° (from methanol-glacial acetic acid), ν_{max} 1660 (CO) cm^{-1}, τ ($CDCl_3$) 1.64-1.84 (2H, m, ArH), 2.17 (1H, s, H-5), 2.48-2.66 (3H, m, ArH), 3.42 (1H, s, H-8), 6.05 (3H, s, $O.CH_3$) and 6.35 (3H, s, $N.CH_3$).

Found: C, 64.0; H, 4.2; N, 9.1%: M^+ 300 (302)

$C_{16}H_{13}ClN_2O_2$ requires: C, 63.9; H, 4.3; N, 9.3%: M 300.5

The methanol mother liquors were concentrated and treated with water (1.0 ml) and methanol (1.0 ml) to give a further crop of the methoxy compound (126d) (0.04 g), m.p. 185° identical (i.r. spectrum) with the first crop.

Evaporation of the aqueous methanol mother liquors gave a brown gummy solid (0.1 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(e) 6-Chloro-7-isopropoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126e)

The quinoxalinium perchlorate (105b) reacted with isopropanol (15 ml) to give 6-chloro-7-isopropoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126e) as pale yellow needles (0.29 g) (49%), m.p. 138° (from ethanol), ν_{max} 1655 (CO) cm^{-1}, τ ($CDCl_3$) 1.65-1.85 (2H, m, ArH), 2.15 (1H, s, H-5), 2.45-2.65 (3H, m, ArH), 3.33 (1H, s, H-8), 5.31 (1H, septet, J 6.3 Hz, CH), 6.34 (3H, s, $N.CH_3$) and 8.54 (6H, d, J 6.3 Hz, CH_3).

Found: C, 65.9; H, 5.0; N, 8.9%

$C_{18}H_{17}ClN_2O_2$ requires: C, 65.8; H, 5.2; N, 8.5%

The isopropanol mother liquors were concentrated and diluted with

water (15 ml) to give a yellow solid (0.15 g) which was crystallised from ethanol to afford a further crop of the isopropoxy compound (126e) (0.10 g) (17%), m.p. 130°, identical (i.r. spectrum) with the first crop.

(f) 1,6-Dimethyl-7-ethoxy-3-phenylquinoxalin-2(1H)-one (126f)

The quinoxalinium perchlorate (105c) reacted with ethanol (30 ml) to give 1,6-dimethyl-7-ethoxy-3-phenylquinoxalin-2(1H)-one (126f) as pale yellow prisms (0.40 g) (68%), m.p. 173° (from ethanol-glacial acetic acid), ν_{max} 1650 (CO) cm^{-1}, τ ($CDCl_3$) 1.64-1.80 (2H, m, ArH), 2.36 (1H, s, H-5), 2.48-2.62 (3H, m, ArH), 3.46 (1H, s, H-8), 5.89 (2H, q, J 7.0 H_3, CH_2), 6.32 (3H, s, N.CH_3), 7.72 (3H, s, CH_3) and 8.51 (3H, t, J 7.0 Hz, CH_3)

Found: C, 73.6; H, 6.1; N, 9.6%

$C_{18}H_{18}N_2O_2$ requires: C, 73.5; H, 6.2; N, 9.5%

The ethanol mother liquors were concentrated, treated with water (10 ml) and extracted with chloroform to give a further crop of the ethoxy compound (126f) (0.08 g), m.p. 168° identical (i.r. spectrum) with the first crop.

(g) 1,6-Dimethyl-7-methoxy-3-phenylquinoxalin-2(1H)-one (126g)

The quinoxalinium perchlorate (105c) reacted with methanol (20 ml) to give 1,6-dimethyl-7-methoxy-3-phenylquinoxalin-2(1H)-one (126g) as yellow prisms (0.30 g) (54%), m.p. 143° (from ethanol), ν_{max} 1650 (CO) cm^{-1}, τ ($CDCl_3$) 1.62-1.80 (2H, m, ArH), 2.35 (1H, s, H-5), 2.46-2.64 (3H, m, ArH), 3.45 (1H, s, H-8), 6.08 (3H, s, O.CH_3), 6.30 (3H, s, N.CH_3) and 7.72 (3H, s, CH_3).

Found: C, 73.3; H, 5.7; N, 10.1%

$C_{17}H_{16}N_2O_2$ requires: C, 72.8; H, 5.7; N, 10.0%

A further crop of the methoxy compound (126g) (0.05 g), m.p. 140° was obtained from the methanol mother liquors on standing, identical

(i.r. spectrum) with the first crop.

The mother liquors were finally concentrated, diluted with water (20 ml) and extracted with chloroform to give a brown gum (0.03 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(h) 7-Ethoxy-6-methoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126h)

A suspension of the quinoxalinium perchlorate (105d) [prepared from 0.56 g, 0.002 mol of the N-oxide (104d)] in the minimum of dry ether (10 ml) was stirred with ethanol (10 ml) at room temperature for 15 min and then heated under reflux on a boiling water bath for 30 min. The reaction mixture was cooled and the solid was collected, washed with water (10 ml) and crystallised (charcoal) from ethanol-glacial acetic acid to give 7-ethoxy-6-methoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126h) as yellow prisms (0.4 g) (64%), m.p. 157°, ν_{max} 1650 (CO) cm^{-1}, τ ($CDCl_3$) 1.62-1.82 (2H, m, ArH), 2.44-2.60 (3H, m, ArH), 2.65 (1H, s, H-5), 3.32 (1H, s, H-8), 5.79 (2H, q, J 7.0 Hz, CH_2), 6.07 (3H, s, $O.CH_3$), 6.30 (3H, s, $N.CH_3$) and 8.45 (3H, t, J 7.0 Hz, CH_3).

Found: C, 69.5; H, 6.0; N, 9.0%

$C_{18}H_{18}N_2O_3$ requires: C, 69.7; H, 5.9; N, 9.5%

The ethanol-ether mother liquors were diluted with ether (100 ml), washed with saturated aqueous hydrogen carbonate solution and evaporated to give a brown gum (0.15 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(i) 6,7-Dimethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126i)

A suspension of the quinoxalinium perchlorate (105d) [prepared from 0.56 g, 0.002 mol of the N-oxide (104d)] in the minimum of dry ether (10 ml) reacted with methanol (10 ml) as described in the previous experiment to give 6,7-dimethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126i) as yellow rectangular prisms (0.40 g) (68%), m.p. 147°

(from ethanol-glacial acetic acid), ν_{max} 1650 (CO) cm^{-1}, τ ($CDCl_3$) 1.60-1.80 (2H, m, ArH), 2.46-2.65 (3H, m, ArH), 2.68 (1H, s, H-5), 3.36 (1H, s, H-8), 6.03 (3H, s, $O.CH_3$), 6.07 (3H, s, $O.CH_3$) and 6.30 (3H, s, $N.CH_3$).

Found: C, 68.4; H, 5.4; N, 9.4%

$C_{17}H_{16}N_2O_3$ requires: C, 68.9; H, 5.4; N, 9.5%

The methanol-ether mother liquors were worked up as described in the previous experiment to give a brown gum (0.06 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(j) 1,6-Dimethyl-7-ethoxymethyl-3-phenylquinoxalin-2(1H)-one (126j)

The quinoxalinium perchlorate (105e) reacted with ethanol (2.5 ml) to give 1,6-dimethyl-7-ethoxymethyl-3-phenylquinoxalin-2(1H)-one (126j) as pale yellow prisms (0.30 g) (49%), m.p. 143° (from ethanol), ν_{max} 1645 (CO) cm^{-1}, τ ($CDCl_3$) 1.62-1.76 (2H, m, ArH), 2.32 (1H, s, H-5), 2.48-2.60 (3H, m, ArH), 2.65 (1H, s, H-8), 5.43 (2H, s, CH_2), 6.28 (3H, s, $N.CH_3$), 6.35 (2H, q, J 7.0 Hz, CH_2), 7.65 (3H, s, CH_3) and 8.70 (3H, t, J 7.0 Hz, CH_3).

Found: C, 74.3; H, 6.7; N, 9.2%

$C_{19}H_{20}N_2O_2$ requires: C, 74.0; H, 6.5; N, 9.1%

The ethanol mother liquors were diluted with water (10 ml) and extracted with chloroform. The extract was washed with saturated aqueous sodium hydrogen carbonate (5.0 ml), water and evaporated to give an intractable brown gum (0.08 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(k) 1,6-Dimethyl-7-methoxymethyl-3-phenylquinoxalin-2(1H)-one (126k)

The quinoxalinium perchlorate (105e) reacted with methanol (2.5 ml) to give 1,6-dimethyl-7-methoxymethyl-3-phenylquinoxalin-2(1H)-one (126k) as pale yellow prisms (0.28 g) (43%), m.p. 172° (from ethanol),

ν_{max} 1645 (CO) cm^{-1}, τ ($CDCl_3$) 1.62-1.78 (2H, m, ArH), 2.31 (1H, s, H-5), 2.46-2.62 (3H, m, ArH), 2.66 (1H, s, H-8), 5.47 (2H, s, O.CH_2), 6.27 (3H, s, N.CH_3), 6.52 (3H, s, O.CH_3) and 7.66 (3H, s, CH_3).

Found: C, 73.0; H, 6.3; N, 9.5%

$C_{18}H_{18}N_2O_2$ requires: C, 73.4; H, 6.2; N, 9.5%

The methanol mother liquors were diluted with water (10 ml) and extracted with chloroform. The extract was washed with saturated aqueous sodium hydrogen carbonate (10 ml), water and evaporated to give a brown gum (0.06g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(1) 7-Ethoxy-3-phenylquinoxalin-2(1H)-one (1261)

The quinoxalinium perchlorate (105f) reacted with ethanol (50 ml) to give 7-ethoxy-3-phenylquinoxalin-2(1H)-one (1261) as pale yellow needles (0.38 g) (71%), m.p. 225° (from glacial acetic acid), ν_{max} 1650 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.80-2.00 (3H, m, ArH), 2.14-2.44 (3H, m, ArH), 2.67 (1H, dd, J_{ortho} 9.0 Hz, J_{meta} 2.5 Hz, H-6), 2.86 (1H, d, J_{meta} 2.5 Hz, H-8), 5.69 (2H, q, J 7.0 Hz, CH_2) and 8.45 (3H, t, J 7.0 Hz, CH_3).

Found: C, 72.2; H, 5.1; N, 10.7%

$C_{16}H_{14}N_2O_2$ requires: C, 72.2; H, 5.3; N, 10.5%

The ethanol mother liquors were concentrated and treated with water (5.0 ml) to give a yellow solid (0.07 g) which was crystallised from glacial acetic acid to afford a further crop of the ethoxy compound (1261) (0.04 g), m.p. 224° identical (i.r. spectrum) with the initial crop.

Complete evaporation of the mother liquors gave a brown intractable gum (0.02 g).

(m) 7-Methoxy-3-phenylquinoxalin-2(1H)-one (126m)

The quinoxalinium perchlorate (105f) reacted with methanol (70 ml) to give 7-methoxy-3-phenylquinoxalin-2(1H)-one (126m) as pale yellow needles (0.37 g) (73%), m.p. 240° (from glacial acetic acid), ν_{max} 1665-1660 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.76-2.00 (3H, m, ArH), 2.10-2.40 (3H, m, ArH), 2.65 (1H, dd, J_{ortho} 9.0 Hz, J_{meta} 2.5 Hz, H-6), 2.82 (1H, d, J_{meta} 2.5 Hz, H-8) and 5.92 (3H, s, $O.CH_3$).

Found: C, 71.0; H, 4.7; N, 11.0%

$C_{15}H_{12}N_2O_2$ requires: C, 71.4; H, 4.8; N, 11.1%

The methanol mother liquors were concentrated and treated with water (5.0 ml) to give a yellow solid (0.07 g) which was crystallised from glacial acetic acid to give a further crop of the methoxy compound (126m) (0.04 g), m.p. 233° identical (i.r. spectrum) with the first crop.

(n) 6-Chloro-7-ethoxy-3-phenylquinoxalin-2(1H)-one (126n)

The quinoxalinium perchlorate (105g) reacted with ethanol (50 ml) to give 6-chloro-7-ethoxy-3-phenylquinoxalin-2(1H)-one (126n) as pale yellow needles (0.14 g) (23%), m.p. 279° (from glacial acetic acid), ν_{max} 1660 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.72-1.92 (3H, m, ArH), 2.08-2.40 (3H, m, ArH), 2.78 (1H, s, H-8), 5.62 (2H, q, J 7.0 Hz, CH_2) and 8.36 (3H, t, J 7.0 Hz, CH_3).

Found: C, 63.7; H, 4.3; N, 9.6%: M^+ 300 (302)

$C_{16}H_{13}ClN_2O_2$ requires: C, 63.9; H, 4.3; N, 9.3%: M 300.5

The ethanol mother liquors were concentrated and treated with water (5.0 ml) to give a yellow solid (0.27 g) which was crystallised from aqueous acetic acid to give a further crop of the ethoxy compound (126n) (0.20 g) (33%), m.p. 270° identical (i.r. spectrum) with the first crop.

Complete evaporation of the mother liquors gave a gummy solid (0.04 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(o) 6-Chloro-7-methoxy-3-phenylquinoxalin-2(1H)-one (126o)

The quinoxalinium perchlorate (105g) reacted with methanol (110 ml) to give 6-chloro-7-methoxy-3-phenylquinoxalin-2(1H)-one (126o) as pale yellow needles (0.24 g) (42%), m.p. 280° (from glacial acetic acid), ν_{max} 1660 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.73-1.93 (3H, m, ArH), 2.03-2.40 (3H, m, ArH), 2.75 (1H, s, H-8) and 5.86 (3H, s, $O.CH_3$).

Found: C, 62.8; H, 3.8; N, 9.8%

$C_{15}H_{11}ClN_2O_2$ requires: C, 62.8; H, 3.8; N, 9.8%

The methanol mother liquors were concentrated and treated with water (5.0 ml) to yield a further crop of the methoxy compound (126o) (0.19 g) (33%), m.p. 271° identical (i.r. spectrum) with the first crop.

(p) 7-Ethoxy-6-methyl-3-phenylquinoxalin-2(1H)-one (126p)

The quinoxalinium perchlorate (105h) reacted with ethanol (25 ml) to give 7-ethoxy-6-methyl-3-phenylquinoxalin-2(1H)-one (126p) as pale yellow prisms (0.40 g) (71%), m.p. 254° (from glacial acetic acid), ν_{max} 1660 (CO), τ ($CF_3.CO_2H$) 1.80-2.44 (6H, m, ArH), 2.88 (1H, s, H-8), 5.66 (2H, q, J 7.0 Hz, CH_2), 7.55 (3H, s, CH_3) and 8.39 (3H, t, J 7.0 Hz, CH_3).

Found: C, 73.0; H, 5.8; N, 9.8%

$C_{17}H_{16}N_2O_2$ requires: C, 72.8; H, 5.8; N, 10.0%

The ethanol mother liquors were concentrated and treated with water (2.0 ml) to give a further crop of the ethoxy compound (126p) (0.09 g) (16%), m.p. 246° identical (i.r. spectrum) with the material obtained before.

(q) 7-Methoxy-6-methyl-3-phenylquinoxalin-2(1H)-one (126q)

The quinoxalinium perchlorate (105h) reacted with methanol (25 ml) to give 7-methoxy-6-methyl-3-phenylquinoxalin-2(1H)-one (126q) as yellow prisms (0.47 g) (88%), m.p. 271° (from glacial acetic acid), ν_{max} 1660 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.76-2.44 (6H, m, ArH), 2.86 (1H, s, H-8), 5.89 (3H, s, $O.CH_3$) and 7.56 (3H, s, CH_3).

Found: C, 72.5; H, 5.4; N, 10.6%.

$C_{16}H_{14}N_2O_2$ requires: C, 72.2; H, 5.3; N, 10.5%.

The methanol mother liquors were concentrated and treated with water (2.0 ml) to give a further crop of the methoxy compound (126q) (0.04 g), m.p. 267°, identical (i.r. spectrum) with the first crop.

(r) 7-Ethoxy-6-methoxy-3-phenylquinoxalin-2(1H)-one (126r)

The quinoxalinium perchlorate (105i) reacted with ethanol (160 ml) to give 7-ethoxy-6-methoxy-3-phenylquinoxalin-2(1H)-one (126r) as yellow prisms (0.25 g) (42%), m.p. 263° (from glacial acetic acid), ν_{max} 1660 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.74-1.94 (2H, m, ArH), 2.12-2.42 (4H, m, ArH), 2.74 (1H, s, H-8), 5.58 (2H, q, J 7.0 Hz, CH_2), 5.88 (3H, s, $O.CH_3$) and 8.40 (3H, t, J 7.0 Hz, CH_3).

Found: C, 68.3; H, 5.4; N, 9.4%

$C_{17}H_{16}N_2O_3$ requires: C, 68.9; H, 5.4; N, 9.4%

The ethanol mother liquors were concentrated and treated with water (5.0 ml) to give a solid (0.2 g) which was crystallised from glacial acetic acid to yield a further crop of the ethoxy compound (126r) (0.15 g) (25%), m.p. 255° identical (i.r. spectrum) with the first crop.

(s) 6,7-Dimethoxy-3-phenylquinoxalin-2(1H)-one (126s)

The quinoxalinium perchlorate (105i) reacted with methanol (150 ml) to give 6,7-dimethoxy-3-phenylquinoxalin-2(1H)-one (126s)

as pale yellow prisms (0.28 g) (50%), m.p. 255° (from glacial acetic acid), ν_{max} 1660 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.70-1.90 (2H, m, ArH), 2.10-2.42 (4H, m, ArH), 2.70 (1H, s, H-8), 5.82 (3H, s, $O.CH_3$) and 5.88 (3H, s, $O.CH_3$).

Found: C, 68.1; H, 5.0; N, 10.1%

$C_{16}H_{14}N_2O_3$ requires: C, 68.1; H, 5.0; N, 9.9%

The methanol mother liquors were concentrated to 40 ml giving a further crop of the methoxy compound (126s) (0.07 g), m.p. 254°, identical (i.r. spectrum) with the initial crop. Complete evaporation of the mother liquors gave a brown intractable gum (0.1 g).

(t) 7-Ethoxymethyl-6-methyl-3-phenylquinoxalin-2(1H)-one (126t)

The quinoxalinium perchlorate (105j) reacted with ethanol (20 ml) to give 7-ethoxymethyl-6-methyl-3-phenylquinoxalin-2(1H)-one (126t) as pale yellow prisms (0.22 g) (37%), m.p. 218° (from glacial acetic acid), ν_{max} 1660 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.68-2.40 (7H, m, ArH), 5.02 (2H, s, $O.CH_2$), 6.02 (2H, q, J 7.0 Hz, $O.CH_2$), 7.44 (3H, s, CH_3) and 8.54 (3H, t, J 7.0 Hz, CH_3).

Found: C, 73.6; H, 6.2; N, 9.4%

$C_{18}H_{18}N_2O_2$ requires: C, 73.5; H, 6.2; N, 9.5%

The ethanol mother liquors were concentrated to give a further crop (0.04 g) of the ethoxymethyl compound (126t) m.p. 215°, identical (i.r. spectrum) with the first crop.

(u) 6,7-Dimethyl-5-methoxy-3-phenylquinoxalin-2(1H)-one (129)

The quinoxalinium perchlorate (105j) reacted with methanol (20 ml) to give 6,7-dimethyl-5-methoxy-3-phenylquinoxalin-2(1H)-one (129) as yellow prisms (0.20 g) (36%), m.p. 279° (from glacial acetic acid), ν_{max} 1650 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.66-2.40 (6H, m, ArH), 5.90 (3H, s, $O.CH_3$) and 7.48 (6H, s, CH_3).

Found: C, 72.8; H, 5.9; N, 10.0%: M^+ 280

$C_{17}H_{16}N_2O_2$ requires: C, 72.8; H, 5.8; N, 10.0%: M 280

The methanol mother liquors were concentrated to give a yellow solid (0.09 g) which was crystallised from glacial acetic acid to yield a further crop of the methoxy compound (129) (0.05 g) (9%), m.p. 272°, identical (i.r. spectrum) with the initial crop.

Complete evaporation of the mother liquors gave a brown intractable gum (0.04 g).

(v) 1-N-Acetoxy-7-ethoxy-3-phenylquinoxalin-2(1H)-one (131a)

The quinoxalinium perchlorate (107a) reacted with ethanol (20 ml) to give 1-N-acetoxy-7-ethoxy-3-phenylquinoxalin-2(1H)-one (131a) as pale yellow needles (0.2 g) (31%), m.p. 147° (from ethanol), ν_{max} 1795 (N.OAc) and 1670 (CO) cm^{-1}, τ ($CDCl_3$) 1.60-1.76 (2H, m, ArH), 2.15 (1H, d, J_{ortho} 9.0 Hz, H-5), 2.44-2.64 (3H, m, ArH), 3.07 (1H, dd, J_{ortho} 9.0 Hz, J_{meta} 2.5 Hz, H-6), 3.37 (1H, d, J_{meta} 2.5 Hz, H-8), 5.89 (2H, q, J 7.0 Hz, O.CH_2), 7.50 (3H, s, N.OAc) and 8.55 (3H, t, J 7.0 Hz, CH_3).

Found: C, 66.3; H, 4.8; N, 8.9%: M^+ 324

$C_{18}H_{16}N_2O_4$ requires: C, 66.7; H, 5.0; N, 8.6%: M 324

The ethanol mother liquors were concentrated at room temperature to give a yellow solid which was collected and washed with water (10 ml) to give 7-ethoxy-1-N-hydroxy-3-phenylquinoxalin-2(1H)-one (131b) as yellow prisms (0.15 g) (27%), m.p. 178° (from ethanol-glacial acetic acid), ν_{max} 3100-2600 br (OH), 1600 (CO) cm^{-1}, τ($CDCl_3$) 1.50-1.78 (2H, m, ArH), 2.14 (1H, d, J_{ortho} 9.0 Hz, H-5), 2.46-2.66 (3H, m, ArH), 2.82-3.96 (2H, m, ArH), 5.80 (2H, q, J 7.0 Hz, CH_2) and 8.52 (3H, t, J 7.0 Hz, CH_3).

Found: C, 67.6; H, 5.0; N, 9.7%: M^+ 282

$C_{16}H_{14}N_2O_3$ requires: C, 68.1; H, 5.0; N, 9.9%: M 282.

The N-hydroxy compound (131b) gave a deep red colour with ferric chloride in ethanol.

(w) 1-N-Acetoxy-7-methoxy-3-phenylquinoxalin-2(1H)-one (131c)

The quinoxalinium perchlorate (107a) reacted with methanol (5.0 ml) to give 1-N-acetoxy-7-methoxy-3-phenylquinoxalin-2(1H)-one (131c) as yellow needles (0.31 g) (50%), m.p. 157° (from ethanol), ν_{max} 1795 (N.OAc) and 1680 (CO) cm^{-1}, τ ($CDCl_3$) 1.60-1.76 (2H, m, ArH), 2.14 (1H, d, J_{ortho} 9.0 Hz, H-5), 2.40-2.60 (3H, m, ArH), 3.06 (1H, dd, J_{ortho} 9.0 Hz, J_{meta} 2.5 Hz, H-6), 3.37 (1H, d, J_{meta} 2.5 Hz, H-8), 6.13 (3H, s, O.CH_3) and 7.52 (3H, s, N.OAc).

Found: C, 65.3; H, 4.5; N, 8.9%: M^+ 310

$C_{17}H_{14}N_2O_4$ requires: C, 65.8; H, 4.5; N, 9.0%: M 310

The methanol mother liquors were concentrated at room temperature to give a yellow solid which was collected and washed with water (10 ml) to give 1-N-hydroxy-7-methoxy-3-phenylquinoxalin-2(1H)-one (131d) as yellow prism (0.1 g) (19%), m.p. 202° (from ethanol-glacial acetic acid), ν_{max} 3100-2700 br (OH) and 1640-1620 (CO) cm^{-1}, τ ($CDCl_3$) 1.45-1.76 (3H, m, ArH), 2.00-2.64 (5H, m, ArH) and 6.05 (3H, s, O.CH_3).

Found: C, 66.9; H, 4.4; N, 10.5%: M^+ 268

$C_{15}H_{12}N_2O_3$ requires: C, 67.2; H, 4.5; N, 10.4%: M 268.

The N-hydroxy compound (131d) gave a deep red colour with ferric chloride in ethanol.

(x) 5-Ethoxy-1-N-hydroxy-7-methyl-3-phenylquinoxalin-2(1H)-one (131e)

The quinoxalinium perchlorate (107b) [prepared from 2.14 g,

0.008 mol of the N-oxide (106b)] reacted with ethanol (5.0 ml) to give 5-ethoxy-1-N-hydroxy-7-methyl-3-phenylquinoxalin-2(1H)-one (131e) as yellow prisms (0.40 g) (17%), m.p. 185° (from ethanol-glacial acetic acid), ν_{max} 3200 br (OH) and 1640 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.74-2.54 (7H, m, ArH), 5.73 (2H, q, J 7.0 Hz, CH_2), 7.38 (3H, s, CH_3) and 8.40 (3H, t, J 7.0 Hz, CH_3).

Found: C, 68.9; H, 5.5; N, 9.3%: M^+ 296

$C_{17}H_{16}N_2O_3$ requires: C, 68.9; H, 5.4; N, 9.4%: M 296.

The ethanol mother liquors were diluted with water (20 ml) and extracted with chloroform. The extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to give a brown gum (0.85 g) which on trituration with ether gave 7-ethoxy-methyl-1-N-hydroxy-3-phenylquinoxalin-2(1H)-one (131f) as yellow prisms (0.29 g),(12%), m.p. 140°, ν_{max} 3150 br (OH) and 1640 (CO) cm^{-1}, τ($CF_3.CO_2H$) 1.60-2.44 (8H, m, ArH), 4.96 (2H, s, $O.CH_2$), 6.05 (2H, q, J 7.0 Hz, $O.CH_2$) and 8.55 (2H, t, J 7.0 Hz, CH_3).

Found: C, 68.4; H, 5.4; N, 9.3%: M^+ 296

$C_{17}H_{16}N_2O_3$ requires: C, 68.9; H, 5.4; N, 9.4%: M 296

The compounds (131 e and f) gave a deep red colour with ferric chloride in ethanol.

The Attempted Reaction of 4-N-Acetoxy-6-chloro-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalinium Perchlorate (105b) with Phenol

A suspension of the quinoxalinium perchlorate (105b) [prepared from 0.50 g, 0.0018 mol of the N-oxide (104b)] in dry ether (100 ml) was treated with phenol (0.75 g), 0.008 mol). The mixture was stirred vigorously at room temperature for 1 h and then filtered. The yellow solid obtained was dissolved in ethanol (30 ml) and the solution was heated under reflux on a boiling water bath for 0.5 h.

The reaction mixture was allowed to cool and the yellow solid which crystallised out was collected to give 6-chloro-7-ethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126c) (0.33 g) (60%), m.p. 180°, identical (i.r. spectrum) with a sample obtained before. The ethanol mother liquors were evaporated and the solid (0.08 g) which was obtained was crystallised from ethanol to give a further crop of the 7-ethoxy compound (126c) (0.03 g) m.p. 179°, identical (i.r. spectrum) with the first crop.

The ether mother liquors were washed with water (10 ml) and evaporated to give phenol (0.70 g), identical (i.r. spectrum) with an authentic sample.

3.5 The Reactions of Quinoxalinium Perchlorates with Amines.

General Method for Reactions in Acetonitrile

A solution of the quinoxalinium perchlorate (105) [prepared from 0.002 mol of the corresponding N-oxide (104)] in acetonitrile (25 ml) was added dropwise with stirring at room temperature to a solution of the amine (0.008 mol) in acetonitrile (10 ml). The mixture was stirred at room temperature for 1 h, concentrated under reduced pressure almost to dryness and treated with water (10 ml). The gummy residue obtained was extracted into chloroform and the extract (A) was washed with 5M aqueous sodium hydroxide solution and evaporated to yield gums which were purified as described in the individual reactions.

The alkaline washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform (B).

I. Reactions of Quinoxalinium Perchlorates with Primary Amines

(a) Methylamine

The perchlorate (105a) was reacted with 25% w/v aqueous

methylamine in acetonitrile as described in the general method (page 103). The chloroform extract (A) gave a brown gum (0.33 g) which was shown by t.l.c. (chloroform) to be a two component mixture and was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave 1-methyl-3-phenylquinoxalin-2(1H)-one (110a) (0.11 g) (23%), m.p. 137° (from ethanol) (lit.[46] 139°), identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene afforded the N-oxide (104a) (0.10 g) (20%), m.p. 194° (from ethanol) (lit.[40] 196°), identical (i.r. spectrum) with an authentic sample.[14]

The chloroform extract (B) gave the 7-hydroxy compound (115h) (0.04 g) (8%), m.p. 302° (lit.[14,38] 300°) identical (i.r. spectrum) with an authentic sample.[14]

(b) Ethylamine

(i) The perchlorate (105a) was reacted with ethylamine in acetonitrile as described in the general method (page 103). The chloroform extract (A) gave a brown gum (0.28 g) which was shown by t.l.c. (chloroform) to be a two component mixture and was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave 1-methyl-3-phenylquinoxalin-2(1H)-one (110a) (0.08 g) (17%), m.p. 138° (from ethanol) (lit.[46] 139°) identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene afforded the N-oxide (104a) (0.02 g) (4%), m.p. 196° (lit.[40] 196°) identical (i.r. spectrum) with an authentic sample.[14] Further elution with ether and chloroform gave unidentified gums (0.07 g).

The chloroform extract (B) gave the 7-hydroxy compound (115h) (0.04 g) (8%), m.p. 300° (lit.[14,38] 300°) identical (i.r. spectrum) with an authentic sample.[14]

(ii) The perchlorate (105b) was reacted with ethylamine in acetonitrile as described in the general method (page 103). The chloroform extract (B) gave a yellow solid (0.4 g) which was shown by t.l.c. (chloroform) to be a two component mixture and was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (110b) (0.06 g) (12%), m.p. 160° (lit.[14] 162°), identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene gave the N-oxide (104b) (0.27 g) (47%), m.p. 187° (lit.[14] 189°) identical (i.r. spectrum) with an authentic sample.[14] Further elution with ether and chloroform gave unidentified gums (0.03 g).

The chloroform extract (B) gave the 7-hydroxy compound (115g) (0.03 g) (6%), m.p. 255° (from glacial acetic acid), identical (i.r. spectrum) with a sample obtained previously.

(iii) The quinoxalinium perchlorate (105g) was reacted with ethylamine in acetonitrile using the quantities given in the general method (page 103). The mixture was stirred at room temperature for 1 h and the yellow solid which separated out was collected and crystallised from glacial acetic acid to give the N-oxide (104g) (0.31 g) (57%), m.p. 302° (from glacial acetical acid) (lit.[41] 313°) identical (i.r. spectrum) with an authentic sample.[14]

The acetonitrile mother liquors were concentrated and treated with water (10 ml) to give a yellow solid (0.08 g) which was shown by t.l.c. (methanol) to be a multicomponent mixture. The aqueous

washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform but gave no further material.

(c) Aniline

The perchlorate (105b) was reacted with aniline in acetonitrile as described in the general method (page 103). The chloroform extract (A) was washed with 5M aqueous hydrochloric acid (2 x 25 ml) and evaporated to give a brown gum (0.45 g) which was shown by t.l.c (chloroform) to be a two component mixture and was chromatographed on alumina.

Elution with light petroleum-toluene (2:1) gave 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (110b) (0.08 g) (14%), m.p. 161° (lit.[14] 162°) identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene gave the N-oxide (104b) (0.27 g) (47%), m.p. 188° (lit.[14] 189°) identical (i.r. spectrum) with an authentic sample.[14]

The hydrochloric acid washings were basified with aqueous sodium hydroxide solution and extracted with chloroform to give aniline (0.48 g) identical (i.r. spectrum) with an authentic sample.

The chloroform extract (B) gave the 7-hydroxy compound (115g) (0.04 g) (7%), m.p. 254°, identical (i.r. spectrum) with a sample obtained previously.

II. Reactions of Quinoxalinium Perchlorates with Secondary Amines

(a) Diethylamine

(1) Diethylamine as solvent

(i) The quinoxalinium perchlorate (105a) [prepared from 2.02 g, 0.008 mol of the N-oxide (104a)] was treated with diethylamine (50 ml) and a vigorous reaction took place. The reaction mixture was heated under reflux on a boiling water bath for 0.5 h, concentrated

under reduced pressure and treated with water (10 ml). The residue was extracted into chloroform and washed with 5M aqueous sodium hydroxide solution (20 ml). The chloroform extract was evaporated to give a brown gum (1.25 g) which was shown by t.l.c. (chloroform) to be a two component mixture. Trituration of the gum with ether-light petroleum (1:1) gave 7-diethylamino-1-methyl-2-phenylquinoxalin-2(1H)-one (134a) as yellow prisms (0.15 g) (6%), m.p. 153° (from ethanol), ν_{max} 1650 (CO) cm^{-1}, $\tau(CDCl_3)$ 1.66-1.80 (2H, m, ArH), 2.30 (1H, d, J_{ortho} 9.0 Hz, H-5), 2.50-2.68 (3H, m, ArH), 3.28 (1H, dd, J_{ortho} 9.0 Hz, J_{meta} 2.5 Hz, H-6), 3.74 (1H, d, J_{meta} 2.5 Hz, H-8), 6.32 (3H, s, $N.CH_3$), 6.51 (4H, q, J 7.0 Hz, CH_2) and 8.76 (6H, t, J 7.0 Hz, CH_3).

Found: C, 74.3; H, 6.7; N, 13.9%: M^+ 307

$C_{19}H_{21}N_3O$ requires: C, 74.3; H, 6.8; N, 13.7%: M 307.

The ether-light petroleum (1:1) was evaporated to give an intractable brown gum (0.9 g).

The alkaline washings were acidified with 5M aqueous hydrochloric acid and the precipitate was collected to give the 7-hydroxy compound (115h) (0.45 g) (22%), m.p. 300° (from glacial acetic acid) (lit.[14,38] 300°) identical (i.r. spectrum) with an authentic sample.[14]

(ii) Diethylamine (25 ml) was cooled in an ice bath and the quinoxalinium perchlorate (105e) [prepared from 2.24 g, 0.008 mol of the N-oxide (104e)] was added in portions with stirring. The reaction mixture was stirred at room temperature for 1 h, concentrated and treated with water (10 ml). Chloroform (C) (50 ml) was added and the aqueous phase was separated, acidified with 5M aqueous hydrochloric acid and allowed to stand for 12 h. The yellow solid which separated from the acidic solution was collected to yield 7-diethyl-

amino-3-phenyl-1,6,8-trimethylquinoxalin-2(1H)-one (143) as yellow prisms (0.53 g) (20%), m.p. 112° (from ethanol), ν_{max} 1645 (CO) cm^{-1}, τ ($CDCl_3$) 1.60-1.78 (2H, m, ArH), 2.40 (1H, s, H-5), 2.46-2.64 (3H, m, ArH), 6.01 (3H, s, $N.CH_3$), 6.81 (4H, q, J 7.0 Hz, CH_2), 7.68 (3H, s, CH_3), 7.74 (3H, s, CH_3) and 9.01 (6H, t, J 7.0 Hz, CH_3).

Found: C, 75.0; H, 7.5; N, 12.4%: M^+ 335

$C_{21}H_{25}N_3O$ requires: C, 75.2; H, 7.5; N, 12.5%: M 335.

The chloroform was washed with 5M aqueous hydrochloric acid (10 ml) and evaporated to give a brown gum (0.94 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture and was chromatographed on alumina.

Elution with light petroleum-toluene (2:1) gave an unidentified yellow solid (0.02 g), m.p. 85-100°, ν_{max} 1660 (CO) cm^{-1}, τ ($CDCl_3$) 1.54 (2H, m, ArH), 2.54 (3H, m, ArH), 3.06 (1H, s, ArH), 6.30 (3H, s, $N.CH_3$), 6.56 (3H, q, J 7.0 Hz, CH_2), 7.58 (3H, s, CH_3), 7.63 (3H, s, CH_3) and 9.04 (6H, t, J 7.0 Hz, CH_3).

Elution with toluene-light petroleum (2:1) gave an unidentified yellow solid (0.09 g) m.p. 135-165°, ν_{max} 1640 (CO) cm^{-1}, τ ($CDCl_3$) 1.60-1.80 (3 units, m, ArH), 2.20-2.30 (1 unit, m, ArH), 2.40-2.60 (4 units, m, ArH), 5.24-5.40 (1 units, m, CH_2), 6.24-6.40 (4 units, m, $N.CH_3$) and 7.40-7.80 (6 units, m, CH_3).

Further elution with toluene-light petroleum (2:1) gave unidentified gums (0.29 g) which were shown by t.l.c. (chloroform) to be multicomponent mixtures.

Elution with toluene gave the N-oxide (104e) (0.31 g) (14%), m.p. 200° (lit.[39] 200°), identical (i.r. and ^1H n.m.r. spectra) with an authentic sample.[14]

Elution with ether, chloroform and methanol gave a brown gum

(0.06 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

The hydrochloric acid which was used to wash the chloroform was basified with 5M aqueous sodium hydroxide solution and extracted with chloroform to give a yellow intractable gum (0.04 g).

(iii) The reaction of the perchlorates (105e) with diethylamine was repeated using the conditions described in the previous experiment with the modification that the chloroform extract (C) was washed with 5M aqueous sodium hydroxide solution (10 ml) followed by 5M aqueous hydrochloric acid solution, and evaporated to give a brown gum (1.2 g) which was shown by t.l.c. (chloroform) to be a mixture of the same components as the gum in the previous experiement.

The alkaline washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform. No material was obtained on evaporation of the chloroform.

The acidic washings were basified with 5M aqueous sodium hydroxide solution and extracted with chloroform to give 3,7-bis-diethylamino-3-phenyl-1,6,7-trimethylquinoxalin-2(1H)-one (135a) as colourless rectangular prisms (0.5 g) (15%), m.p. 150° (from ethanol), ν_{max} 1670 (CO) cm^{-1}, τ ($CDCl_3$) 2.32-2.60 (2H, m, ArH), 2.66 (3H, m, ArH), 3.66 (1H, m, olefinic), 4.53 (1H, d, J 3.0 Hz, olefinic), 6.92 (3H, d, J 1.5 Hz, $N.CH_3$), 7.20-7.60 (8H, m, CH_2), 8.02 (3H, d, J 1.5 Hz, CH_3), 8.63 (3H, d, J 3.0 Hz, CH_3), 8.97 (6H, t, J 7.0 Hz, CH_3) and 8.98 (6H, t, J 7.0 Hz, CH_3).

Irradiation on the multiplet at τ 3.66 caused the doublet at τ 8.02 to collapse to a singlet. Irradiation on the doublet at τ 8.02 caused the multiplet at τ 3.66 to collapse to a doublet, J 1.5 Hz.

Found: C, 73.7; H, 9.0; N, 13.8%: M^+ 336

$C_{25}H_{36}N_4O$ requires: C, 73.5; H, 8.9; N, 13.7%: M 408.

(iv) Diethylamine (25 ml) was cooled in an ice bath and the quinxolinium perchlorate (105j) [prepared from 1.06 g, 0.004 mol of the N=oxide (104j)] was added in portions. The mixture was stirred in the ice bath for 15 min, then at room temperature for 15 min and finally heated on a steam bath for 15 min. The solution was cooled and the yellow crystalline solid obtained was collected to yield the N-oxide (104j) (0.09 g) (9%), m.p. 283° (lit.[14] 286°) identical (i.r. spectrum) with an authentic sample.[14]

The diethylamine mother liquors were concentrated, treated with water (5.0 ml) and extracted with chloroform. The extract was washed with 5M aqueous hydrochloric acid (10 ml) and evaporated to give the N-oxide (104j) (0.85 g) (80%), m.p. 286° (from glacial acetic acid), identical (i.r. spectrum) with a sample obtained previously.

The hydrochloric acid washings, adjusted to pH 7 and extracted with chloroform yielded no material.

(v) The perchlorate (105f) [prepared from 0.48 g, 0.002 mol of the N-oxide (104f)] was added in portions with stirring to diethylamine (10 ml) cooled in an ice bath. The reaction mixture was stirred at room temperature for 1 h, concentrated, treated with water (10 ml) and extracted with chloroform. The extract was washed with 5M aqueous hydrochloric acid (2 x 15 ml) and evaporated to give the N-oxide (104f) (0.41 g) (85%), m.p. 284° (from glacial acetic acid) (lit.[40] 285°) identical (i.r. spectrum) with an authentic sample.[14]

The acidic washings were adjusted to pH 7 by the addition of

solid sodium acetate and extracted with chloroform to give 7-diethylamino-3-phenylquinoxalin-2(1H)-one (134c) as yellow elongated prisms (0.05 g) (9%), m.p. 232° (from ethanol-glacial acetic acid), ν_{max} 1660 (CO) cm^{-1}, τ ($CDCl_3$) (60 MHz ^1H n.m.r.) 1.48-1.85 (2H, m, ArH), 2.38 (1H, d, J_{ortho} 9.0 Hz, H-5), 2.50-2.83 (3H, m, ArH), 3.32 (1H, dd, J_{ortho} 9.0 Hz, J_{meta} 2.5 Hz, H-6) 3.62 (1H, d, J_{meta} 2.5 Hz, H-8), 6.56 (4H, q, J 7.0 Hz, CH_2) and 8.80 (6H, t, J 7.0 Hz, CH_3).

Found: C, 73.6; H, 6.5; N, 14.3%: M^+ 293

$C_{18}H_{19}N_3O$ requires: C, 73.7; H, 6.5; N, 14.3%: M 293.

(vi) The quinoxalinium perchlorate (107a) [prepared from 1.01 g, 0.004 mol. of the N-oxide (106a)] was added in portions with stirring to diethylamine (50 ml) cooled in an ice bath. A vigorous reaction immediately took place and a black gummy mixture was obtained. The mixture was stirred at room temperature for 1 h, concentrated, treated with water (5.0 ml) and extracted with chloroform to give a black intractable gum (0.55 g). Trituration of the gum with organic solvents failed to produce any solid material.

(2) Diethylamine in Acetonitrile as Solvent

(i) The quinoxalinium perchlorate (105a) was reacted with diethylamine in acetonitrile as described in the general method (page 103). The chloroform extract (A) gave a yellow solid (0.42 g) which was shown by t.l.c. (chloroform) to be a two component mixture and was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave the 7-diethylamino compound (134a) (0.20 g) (33%), m.p. 153° (from ethanol), identical (i.r. spectrum) with a sample obtained previously.

Elution with toluene afforded the N-oxide (104a) (0.19 g) (38%),

m.p. 194° (lit.[40] 196°), identical (i.r. spectrum) with an authentic sample.[40]

The chloroform extract (B) gave the 7-hydroxy compound (115h) (0.1 g) (20%), m.p. 300° (lit.[14,38] 300°) identical (i.r. spectrum) with an authentic sample.[14]

(ii) The quinoxalinium perchlorate (105b) was reacted with diethylamine in acetonitrile as described in the general method (page 103). The chloroform extract (A) gave a brown gummy solid (0.44 g) which was shown by t.l.c. (chloroform) to be a two component mixture and was chromatographed on alumina.

Elution with toluene-light petroleum (2:1) gave 6-chloro-7-diethylamino-1-methyl-3-phenylquinoxalin-2(1H)-one (134b) as yellow prisms, (0.18 g) (26%), m.p. 83° (from light petroleum), ν_{max} 1650 (CO) cm^{-1}, τ ($CDCl_3$) 1.64-1.82 (2H, m, ArH), 2.09 (1H, s, H-5), 2.44 (3H, m, ArH), 3.18 (1H, s, H-8), 6.30 (3H, s, $N.CH_3$), 6.68 (4H, q, J 7.0 Hz, CH_2) and 8.84 (6H, t, J 7.0 Hz, CH_3).

Found: C, 67.2; H, 5.7; N, 12.1%: M^+ 341 (343)

$C_{19}H_{20}ClN_3O$ requires: C, 66.8; H, 5.9; N, 12.3%: M 341.5

Elution with toluene gave the N-oxide (104b) (0.19 g) (33%), m.p. 189° (from ethanol) (lit.[14] 189°) identical (i.r. spectrum) with an authentic sample.[14]

The chloroform extract (B) gave the 6-chloro-7-hydroxy compound (115g) (0.11 g) (19%), m.p. 250-254°, identical (i.r. spectrum) with a sample obtained previously.

(3) Diethylamine in Ether

A suspension of the perchlorate (105b) [prepared from 1.0 g, 0.0035 mol of the N-oxide (104b)] in dry ether (100 ml) was cooled in an ice bath and treated dropwise with stirring with a solution of

diethylamine (1.16 g, 1.72 ml, 0.008 mol) in dry ether (10 ml). The reaction mixture was stirred at room temperature for 1 h and filtered to remove some insoluble material. The ethereal filtrate was washed with water (10 ml) and 5M aqueous sodium hydroxide solution (10 ml) and evaporated to give a brown gum (0.8 g) which was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (110b) (0.08 g) (9%), m.p. 161° (from ethanol) (lit.[14] 162°) identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene-light petroleum (2:1) gave the 7-diethylamino compound (134b) (0.07 g) (6%), m.p. 83° (from light petroleum), identical (i.r. spectrum) with a sample obtained before.

Elution with toluene gave the N-oxide (104b) (0.18 g) (18%), m.p. 188° (from ethanol) (lit.[14] 189°) identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene-ether (1:1) gave an unidentified yellow solid (0.08 g) m.p. 140-180°, ν_{max} 1660 (CO) cm^{-1}, the t.l.c. (chloroform) of which indicated that it was at least a two component mixture. Elution with methanol failed to produce any further material.

The alkaline washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform to give the 6-chloro-7-hydroxy compound (115g) (0.1 g) (10%), m.p. 256° (from glacial acetic acid), identical (i.r. spectrum) with a sample obtained previously.

The material which was insoluble in the ether was collected and dried to give a colourless solid, 0.40 g, ν_{max} 3300-3100 br (NH) cm^{-1} the i.r. spectrum of which was characteristic of a salt.

The solid was dissolved in water (1.0 ml). Acidification with 5M aqueous sulphuric acid solution failed to cause precipitation of any solid material.

(b) Pyrrolidine

(1) Pyrrolidine in Acetonitrile

The perchlorate (105b) was reacted with pyrrolidine in acetonitrile as described in the general method (page 103). The chloroform extract (A) was washed with 5M aqueous hydrochloric acid (2 x 25 ml) and then evaporated to give a gummy solid which was chromatographed on alumina.

Elution with toluene-light petroleum (2:1) gave 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (110b) (0.05 g) (9%), m.p. 162° (lit.[14] 162°), identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene gave the N-oxide (104b) (0.14 g) (25%) m.p. 195° (lit.[40] 196°), identical (i.r. spectrum) with an authentic sample.[14]

The acidic washings were basified with 5M aqueous sodium hydroxide solution and extracted with chloroform to give a brown oil (0.01 g).

The chloroform extract (B) gave the 7-hydroxy compound (115g) (0.11 g) (19%), m.p. 255° (from glacial acetic acid) identical with a sample obtained before.

(2) Pyrrolidine in Diethyl Ether

A suspension of the perchlorate (105b) [prepared from 0.5 g, 0.0018 mol of the N-oxide (104b)] in dry ether (100 ml) was cooled in an ice bath and treated dropwise with stirring with a solution of pyrrolidine (0.66 ml, 0.008 mol) in dry ether (10 ml). The solution was stirred at room temperature for 1 h and treated with water (10 ml) followed by 5M aqueous hydrochloric acid (5.0 ml).

The ether layer was separated, washed with 5M aqueous sodium hydroxide solution and evaporated to afford a brown gum (0.40 g) which was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave 6,7-dichloro-1-methyl-3-phenylquinoxalin-2(1H)-one (115j) (0.10 g) (18%) m.p. 170° (from ethanol) (lit.[48] 171°) identical (i.r. and ^{1}H n.m.r. spectra) with an authentic sample.[14]

Elution with toluene gave the N-oxide (104b) (0.14 g) (28%), m.p. 189° (from ethanol) (lit.[14] 189°), identical (i.r. spectrum) with an authentic sample.[14]

Acidification of the alkaline washings with 5M aqueous hydrochloric acid and extraction with chloroform gave the 7-hydroxy compound (115g) (0.01 g) m.p. 255°, identical (i.r. spectrum) with a sample obtained previously.

Basification of the acidic washings with 5M aqueous sodium hydroxide and extraction with chloroform yielded no further material.

(c) Morpholine

General Method for Reactions of Quinoxalinium Perchlorates with Morpholine

A suspension of the quinoxalinium perchlorate (105) [prepared from 0.002 mol of the corresponding N-oxide (104)] in dry ether (100 ml) was cooled in an ice bath and treated dropwise with stirring with a solution of morpholine (0.7 ml, 0.008 mol) in dry ether (10 ml). The suspension was stirred at room temperature for 0.5 h and the solid (A) was collected, washed with water (5.0 ml) and dried in vacuo. Work up of the ether mother liquors (B) gave more material as described in the individual reactions.

(i) The perchlorate (105a) was treated with morpholine in dry ether as described in the general method. The solid (A) was collected to give 4-N-acetoxy-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (144a) (0.33 g) (43%), m.p. 86°, ν_{max} 1790 (cyclic N.OAc) and 1690 (CO) cm^{-1}, τ ($CF_3.CO_2H$), 1.60-2.50 (9H, m, ArH), 5.60-6.10 (6H, m, $N.CH_3$, CH_2), 6.20-6.50 (4H, m, CH_2) and 7.64 (3H, s, N.OAc), M^+ 321, (M 381).

The ether mother liquors (C) were washed with saturated aqueous sodium hydrogen carbonate and evaporated to give a brown gum (0.18 g). The gum was extracted into chloroform and washed with 5M aqueous sodium hydroxide solution (10 ml). The chloroform extract was evaporated to give a brown gum (0.12g) which was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave 1-methyl-3-phenylquinoxalin-2(1h)-one (110a) (0.03 g) (6%), m.p. 139° (from ethanol) (lit.[46] 139°) identical (i.r. spectrum) with an authentic sample.

Elution with toluene gave the N-oxide (104a) (0.07 g) (14%), m.p. 194° (lit.[40] 196°), identical (i.r. spectrum) with an authentic sample.[40]

The alkaline washings were acidified with 5M aqueous hydrochloric acid and extracted with chloroform to give the 7-hydroxy compound (115h) (0.06 g) (12%), m.p. 302° (from glacial acetic acid) (lit.[14,38] 300°) identical (i.r. spectrum) with an authentic sample.[14]

(ii) The perchlorate (105b) was treated with morpholine in dry ether as described in the general method. The solid (A) was collected to give 4-N-acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-

2(1H)-one (144b) (0.25 g) (30%), m.p. 108°, ν_{max} 1790 (cyclic N.OAc) and 1690 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.36-2.50 (8H, m, ArH), 5.68-5.88 (4H, m, CH_2), 6.02 (3H, s, $N.CH_3$), 6.28-6.54 (4H, m, CH_2) and 7.76 (3H, s, N.OAc); M^+ 355 (357), (M 415.5).

The ether mother liquors (B) were worked up as described in the previous experiment to give a black gum (0.22 g) which was chromatographed on alumina.

Elution with light petroleum-toluene (1:1) gave 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (110b) (0.05 g) (9%), m.p. 161° (lit.[14] 162°), identical (i.r. spectrum) with an authentic sample.[14]

Elution with toluene gave the N-oxide (104b) (0.06 g) (10%, m.p. 187° (lit.[14] 189°) identical (i.r. spectrum) with an authentic sample.[14]

The alkaline washings afforded the 7-hydroxy compound (115g) (0.06 g) (10%), m.p. 255° (from glacial acetic acid), identical (i.r. spectrum) with a sample obtained previously.

(iii) The perchlorate (105e) was treated with morpholine in dry ether as described in the general method. The solid (A) was collected to yield the N-oxide (104e) (0.05 g) (9%), m.p. 200° (from ethanol) (lit.[39] 200°), identical (i.r. and ^1H n.m.r. spectra) with an authentic sample.[14]

The ether mother liquors (B) were washed with water (20 ml) and evaporated to give a yellow gum (0.51 g) which was chromatographed on alumina.

Elution with toluene gave the N-oxide (104e) (0.10 g) (19%), m.p. 199° (lit.[39] 200°), identical (i.r. spectrum) with an authentic sample.[14] Further elution with toluene gave an unidentified yellow solid (0.06 g) m.p. 105-140°, ν_{max} 1660 (CO) cm^{-1}, τ ($CDCl_3$) 1.50-2.00

(3 units, m, ArH), 2.16-2.90 (8 units, m, ArH), 6.00-6.66 (13 units, m, $N.CH_3$) and 7.30-7.90 (11 units, broad singlet, CH_3).

Elution with ether-chloroform (1:1) gave 3,7-dimorpholino-3-phenyl-1,6,7-trimethylquinoxalin-2(1H)-one (135b) as colourless needles (0.16 g) (18%), m.p. 206° (from ethanol), ν_{max} 1680 (CO) cm^{-1}, τ ($CDCl_3$) 2.40-2.80 (5H, m, ArH), 3.60 (1H, q, J 1.4 Hz, olefinic), 4.51 (1H, s, olefinic), 6.33 (8H, q, J 3.5 Hz, CH_2), 6.92 (3H, s, $N.CH_3$), 7.20-7.70 (8H, m, CH_2), 8.03 (3H, d, J 1.4 Hz, CH_3) and 8.66 (3H, s, CH_3).

Irradiation at τ 8.03 caused the quartet at τ 3.60 to collapse to a singlet. Irradiation at τ 3.60 caused the doublet at τ 8.03 to collapse to a singlet. On expansion to sweep width 250 Hz, the quartet at τ 3.60 appeared to be a double quartet with J 1.4 and 0.2 Hz.

Found: C, 69.0; H, 7.4; N, 12.9%: M^+ 436 (base peak 350)
$C_{25}H_{32}N_4O_3$ requires: C, 68.8; H, 7.4; N, 12.8%: M 436.

Elution with ether gave 1,6-dimethyl-7-hydroxymethyl-3-phenylquinoxalin-2(1H)-one (115d) (0.01 g) (2%), m.p. 132° (from ethanol) (lit.[14] 133°) identical (i.r. spectrum) with an authentic sample.[14]

(iv) The perchlorate (105j) was treated with morpholine in dry ether as described in the general method. The solid (A) was collected to give the N-oxide (104j) (0.32 g) (60%), m.p. 285° (from glacial acetic acid) (lit.[14] 286°), identical (i.r. spectrum) with an authentic sample.[14]

The ether mother liquors (B) were washed with water (5.0 ml) and evaporated to yield a yellow gum (0.20 g) which on trituration with ether afforded a further crop of the N-oxide (104j) (0.03 g), m.p. 280° identical (i.r. spectrum with the first crop. The ether

mother liquors were evaporated to give a yellow gum (0.15 g) which failed to produce any solid material on trituration with organic solvents.

III. Reactions of Quinoxalinium Perchlorates with Tertiary Amines.

(a) Triethylamine

The quinoxalinium perchlorate (105b) reacted with triethylamine in acetonitrile as described in the general method (page 103). The chloroform extract (A) gave a yellow gummy solid (0.45 g) which was chromatographed on alumina. Elution with light petroleum-toluene (1:1) afforded the deoxygenated quinoxalinone (110b) (0.05 g) (9%), m.p. 161° (from ethanol) (lit.[14] 162°), identical (i.r. spectrum) with an authentic sample.[14] Elution with toluene gave the N-oxide (104b) (0.35 g) (65%), m.p. 189° (from ethanol) (lit.[14] 189°) identical (i.r. spectrum) with an authentic sample.[14]

The chloroform extract (B) gave the 7-hydroxy compound (115g) (0.03 g) (6%), m.p. 255°, identical (i.r. spectrum) with a sample obtained previously.

(b) Pyridine

A solution of the perchlorate (105b) [prepared from 0.50 g, 0.0018 mol of the N-oxide (104b)] in acetonitrile (25 ml) was treated at room temperature with dry pyridine (0.63 g, 0.65 ml, 0.008 mol). The reaction mixture was stirred at room temperature for 1 h, concentrated and treated with water (10 ml). The yellow solid which was obtained was collected, washed with water (10 ml) and dried to yield the N-oxide (104b) (0.40 g) (80%), m.p. 186° (from ethanol) (lit.[14] 189°), identical (i.r. spectrum) with an authentic sample.[14]

3.6 Reactions of Quinoxalinone Adducts

(a) Reactions of 4-N-Acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (144b)

(i) With Ethanol

A suspension of the adduct (144b) (0.3 g, 0.0007 mol) in 99% ethanol (50 ml) was stirred at room temperature for 1 h. The reaction mixture was evaporated, extracted into chloroform and washed with 5M aqueous sodium hydroxide solution (2 x 10 ml).

The chloroform extract was evaporated to give a gummy yellow solid (0.16 g) which was chromatographed on alumina.

Elution with toluene gave 6-chloro-7-ethoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (126c) (0.12 g) (53%), m.p. 180°, identical with a sample obtained previously.

The alkaline washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform to yield 6-chloro-7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (115g) (0.08 g) (40%), m.p. 254° identical (i.r. spectrum) with a sample obtained previously.

(ii) With Glacial Acetic Acid

A solution of the adduct (144b) (0.40 g, 0.001 mol) in glacial acetic acid (5.0 ml) at room temperature for 2 h. The yellow solid which crystallised from the reaction mixture was combined with the material obtained by diluting the filtrate with water (15 ml) and dried to yield 7-acetoxy-6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (115b) (0.32 g) (98%), m.p. 175° (lit.[14] 171°) identical (i.r. spectrum) with an authentic sample.[14]

(iii) With Hydrochloric Acid

A suspension of the adduct (144b) (0.10 g, 0.00024 mol) in 5M aqueous hydrochloric acid (1.0 ml) was stirred at room temperature

for 2 h. The solid was collected, washed with water and dried to yield 6,7-dichloro-1-methyl-3-phenylquinoxalin-2(1H)-one (115j) (0.065 g) (83%), m.p. 170° (lit.[48] 171°) identical (i.r. spectrum) with an authentic sample.[14]

Extraction of the aqueous mother liquors with chloroform failed to yield any further material.

(b) Reactions of 3,7-Bis-diethylamino-3-phenyl-1,6,7-trimethylquinoxalin-2(1H)-one (135a)

(i) With Glacial Acetic Acid

The adduct (135a) (0.05 g, 0.00012 mol) was heated under reflux in glacial acetic acid (5.0 ml) for 1 h. The solution was cooled and evaporated to yield 7-acetoxymethyl-1,6-dimethyl-3-phenylquinoxalin-2(1H)-one (115c) (0.03 g) (76%), m.p. 113° (lit.[14] 114°) identical (i.r. and ^{1}H n.m.r. spectra) with an authentic sample.[14]

(ii) With Hydrochloric Acid

The colourless crystalline adduct (135 a) (0.05 g, 0.00012 mol) was dissolved in 5M aqueous hydrochloric acid (1.0 ml) giving a yellow solution which on standing at room temperature for 12 h deposited a yellow crystalline solid which was collected, washed with water and dried *in vacuo* to yield 7-dimethylamino-3-phenyl-1,6,8-trimethylquinoxalin-2(1H)-one (143) (0.03 g) (73%), m.p. 112° (from ethanol) identical with a sample prepared previously.

Extraction of the mother liquors with chloroform failed to produce any further material.

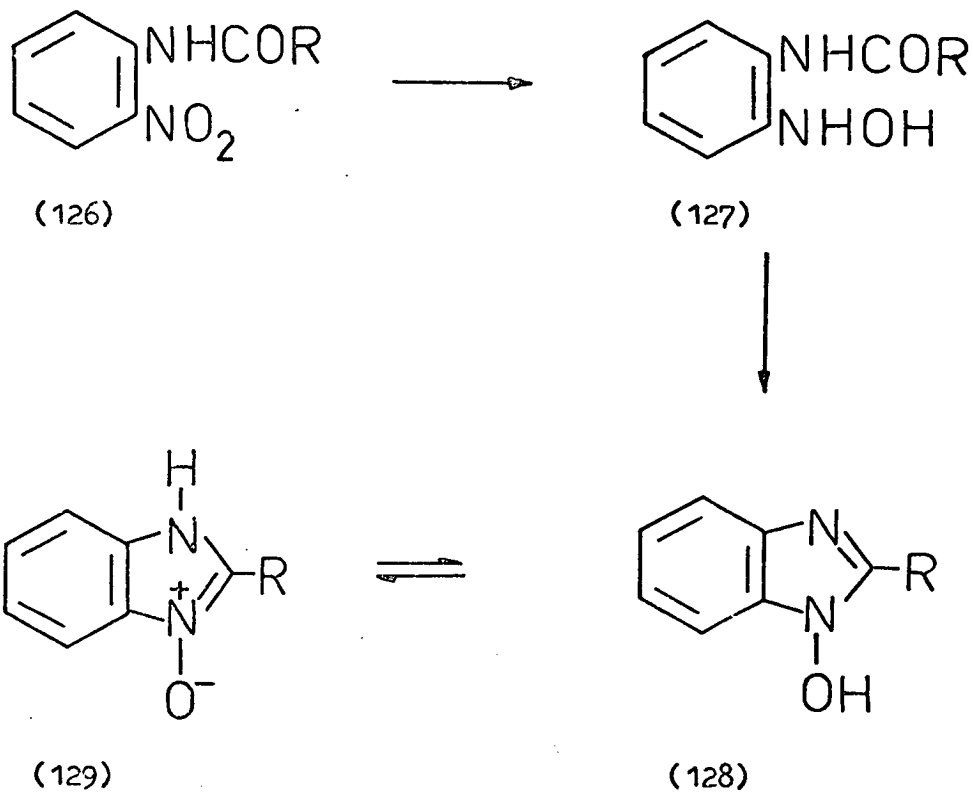
(c) Reaction of 3,7-Dimorpholino-3-phenyl-1,6,7-trimethylquinoxalin-2(1H)-one (135b) With Glacial Acetic Acid

The adduct (135b) (0.05 g, 0.0001 mol) was heated under reflux in glacial acetic acid (5.0 ml) for 1 h. The solution was cooled

and evaporated to yield the 7-acetoxymethyl compound (115c) (0.04 g) (94%), m.p. 114° (lit.[14] 114°) identical (i.r. spectrum) with an authentic sample.[14]

Chapter Four

Some Studies on the Synthesis and Reactivity of N-Oxygenated Benzimidazoles



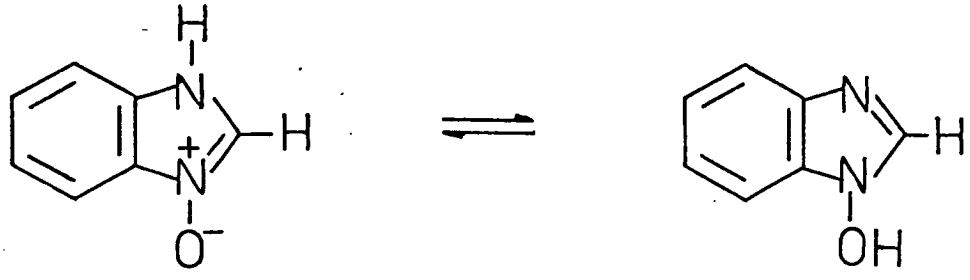
(126) (127) (129) (128)

$R = H, CH_3$

scheme 24

4.1 The Synthesis of N-Oxygenated Benzimidazoles

The synthesis of benzimidazole N-oxides by peracid oxidation of the corresponding benzimidazoles has been unsuccessful[49] and alternative routes to benzimidazole N-oxides are therefore important. It should be noted that in some cases the benzimidazole N-oxides are tautomeric with the N-hydroxybenzimidazole [(124)⇌(125)]. For



(124) (125)

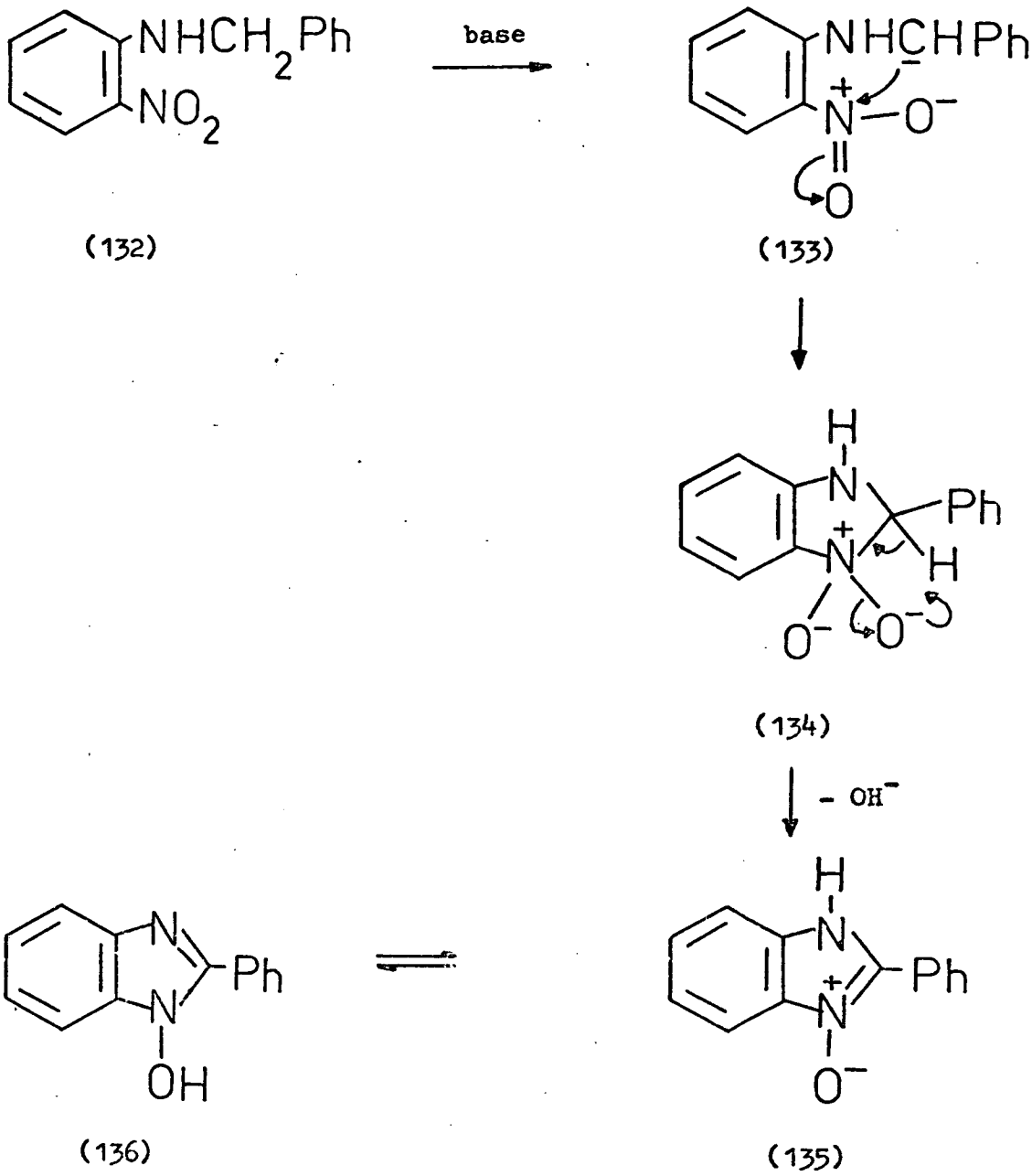
convenience, both tautomeric forms will not be shown in every case.

Some of the methods which have been used for the synthesis of N-oxygenated benzimidazoles are discussed below.

(1) Cyclisation of Nitro Compounds

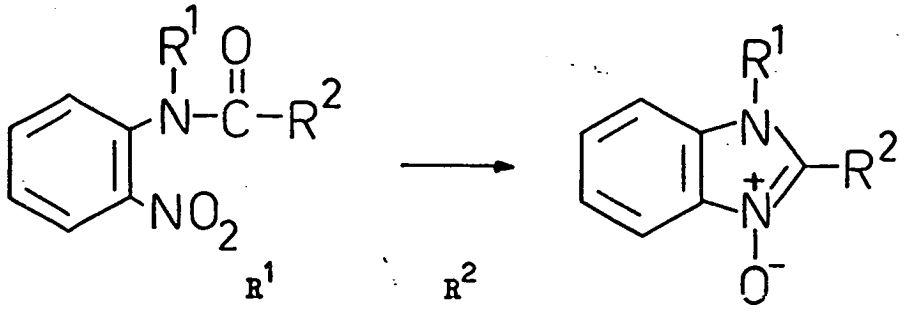
(a) Reductive Cyclisation

Mild reduction of o-nitroanilides (126) gives[50,51] 1-hydroxy-benzimidazoles (128) which are tautomeric with the benzimidazole N-oxides (129). The intermediate in the reaction is probably the phenylhydroxylamine (127) (scheme 24) formed by reduction of the nitro group in the o-nitroanilide (126). Reducing agents used in these cyclisations include zinc and hydrochloric acid, hydrogen and palladium, and hydrogen sulphide in ammonia. N-Substituted anilides (130) likewise cyclise to benzimidazole N-oxides(131) in which tautomerism is not possible.[52]


NHCH2Ph
NO2
base
NHCHPh
N
O
O
(132)
(133)
H
N
Ph
N
H
O
O
(134)
- OH
N
Ph
N
OH
H
N
Ph
N
O
(136)
(135)

scheme 25

It should be noted that 1-hydroxybenzimidazoles containing



	R^1	R^2
(130)	CH_3	CH_3

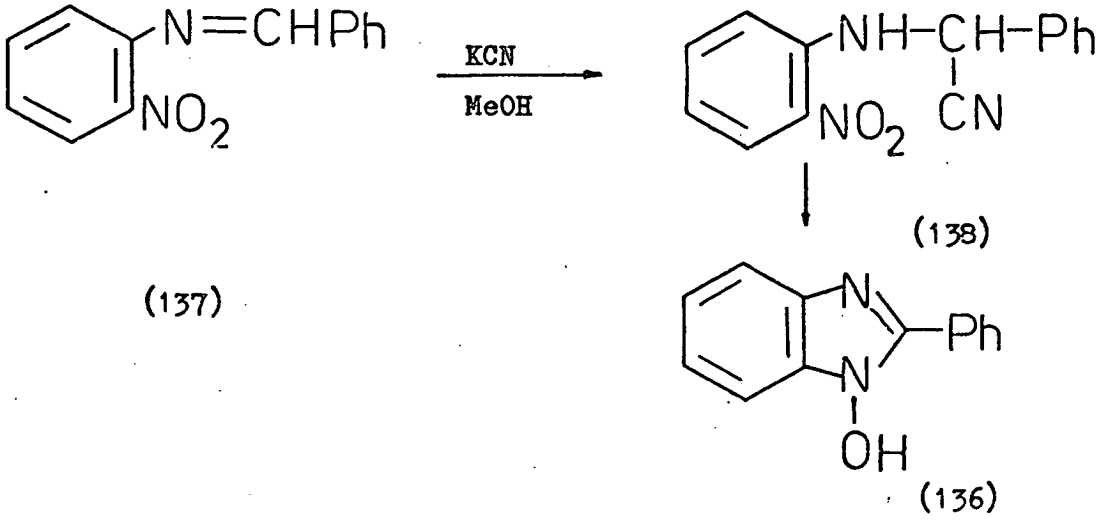
(131)

functional groups in the 2-position cannot be prepared by the reductive cyclisation of nitro compounds.

(b) Base Catalysed Aldol-type Cyclisations

(i) N-Substituted-o-nitroanilines undergo base-catalysed aldol-type cyclisations to yield 1-hydroxybenzimidazoles. For example N-benzyl-o-nitroaniline (132) gives 1-hydroxy-2-phenylbenzimidazole (136) (scheme 25) on heating under reflux in methanolic sodium hydroxide.[53] This reaction probably involves nucleophilic attack on the nitro group by the carbanion centre in the intermediate (133) (scheme 25) to give the intermediate (134). Elimination of hydroxide ion from intermediate (134) gives the benzimidazole N-oxide (135) which is tautomeric with the N-hydroxybenzimidazole (136).

(ii) N-Benzylidene-o-nitroaniline (137) undergoes base catalysed cyclisation to give 1-hydroxy-2-phenylbenzimidazole (136) on treatment with potassium cyanide in methanol.[54] This reaction



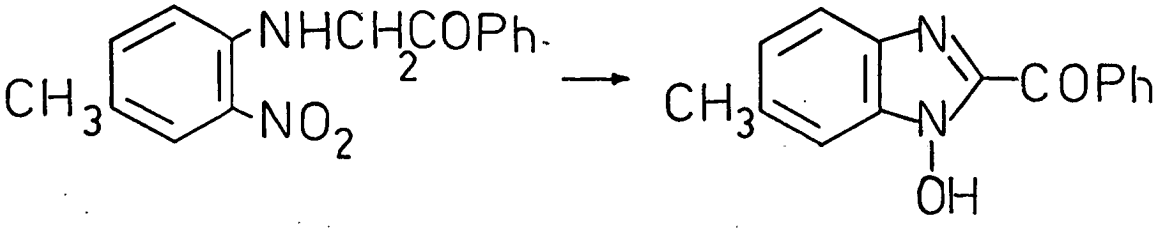
(137)

(138)

(136)

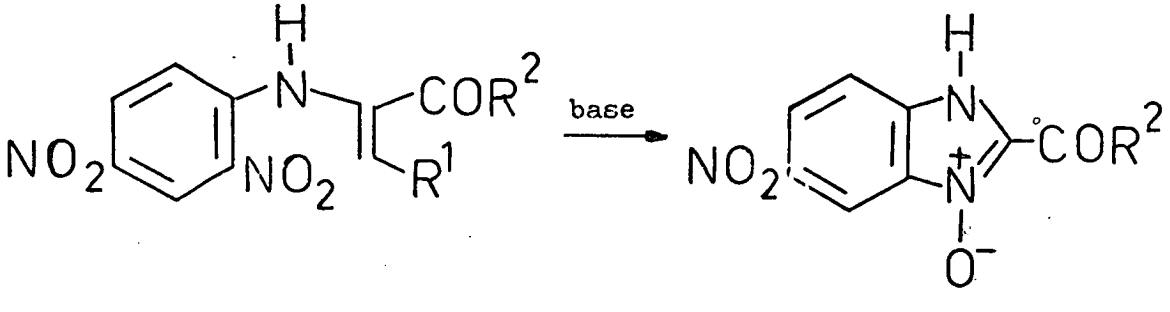
probably goes via the cyano intermediate (138), and is important because the conditions used are much less drastic than in the base catalysed cyclisation (132→136) (scheme 25).

(iii) Another example of an active methylene type cyclisation is the formation of the N-hydroxybenzimidazole (140) from the nitro compound (139).[55]



(139) (140)

(iv) 2,4-Dinitrophenylaminoalkenes (141) also undergo base-catalysed cyclisation[56] to give benzimidazole N-oxides(142). These reactions give high yields of the N-oxides (142) and are usually carried out in polar solvents.

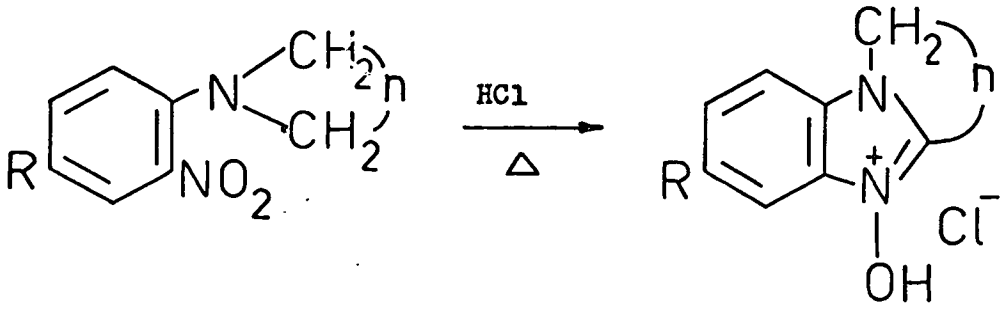


(141) (142)

R^1	R^2
H	OCH_3
CH_3	OCH_3
Ph	OCH_3

(c) Acid Catalysed Cyclisations

N,N-Disubstituted o-nitroanilines (143) undergo intramolecular cyclisation to give the N-oxide hydrochlorides (144) when treated with hot hydrochloric acid[57] (scheme 26). Good yields are obtained



(143) (144)

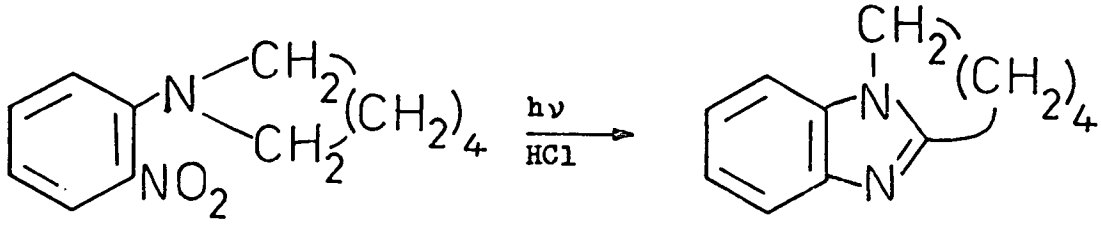
	n	R
(a)	$(CH_2)_2$	H
(b)	CH_2OCH_2	NO_2
(c)	$(CH_2)_4$	H

scheme 26

in these cyclisations and the reaction provides a useful route to benzimidazole N-oxides.

(d) Photochemical Cyclisations

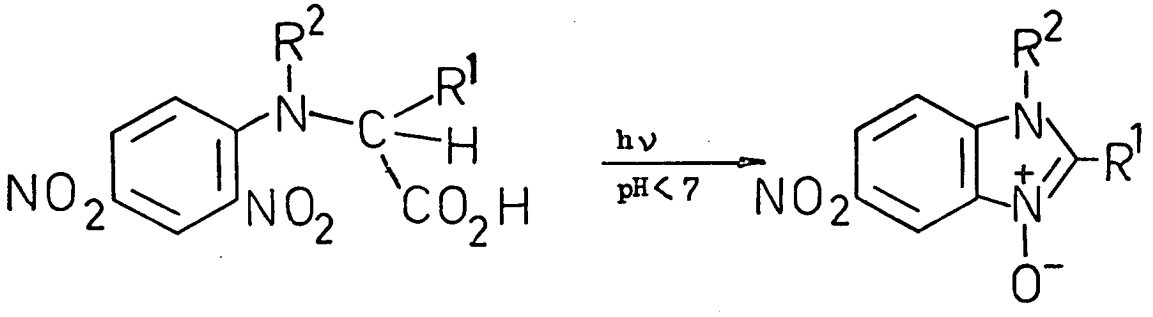
(i) N,N-Disubstituted o-nitroanilines (143) also undergo cyclisation on irradiation in aqueous methanolic hydrogen chloride.[58] The product of the cyclisation is either a benzimidazole N-oxide or a benzimidazole depending on the nature of the amino group and the ring substituents. Thus the amine (143a) undergoes acid-catalysed photochemical cyclisation to give the benzimidazole N-oxide



(143c) (145)

hydrochloride (144a) while the amine (143c) gives the benzimidazole (145).

(ii) N-2,4-Dinitrophenyl derivatives of α-amino acids (146) undergo photochemical cyclisation to give benzimidazole N-oxides (147).[59] These reactions are carried out in aqueous solution at low pH and



(146) (147)

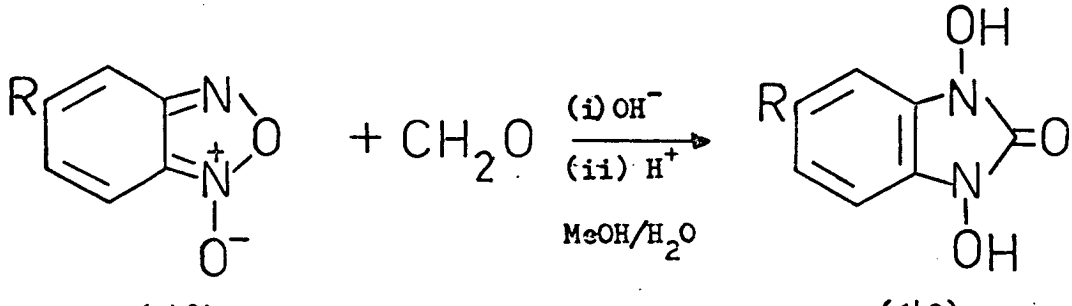
	R^1	R^2
(a)	H	H
(b)	CH_2OH	H
(c)	iso-Bu	H

scheme 27

often give high yields.

(2) Reactions of Benzfuroxans

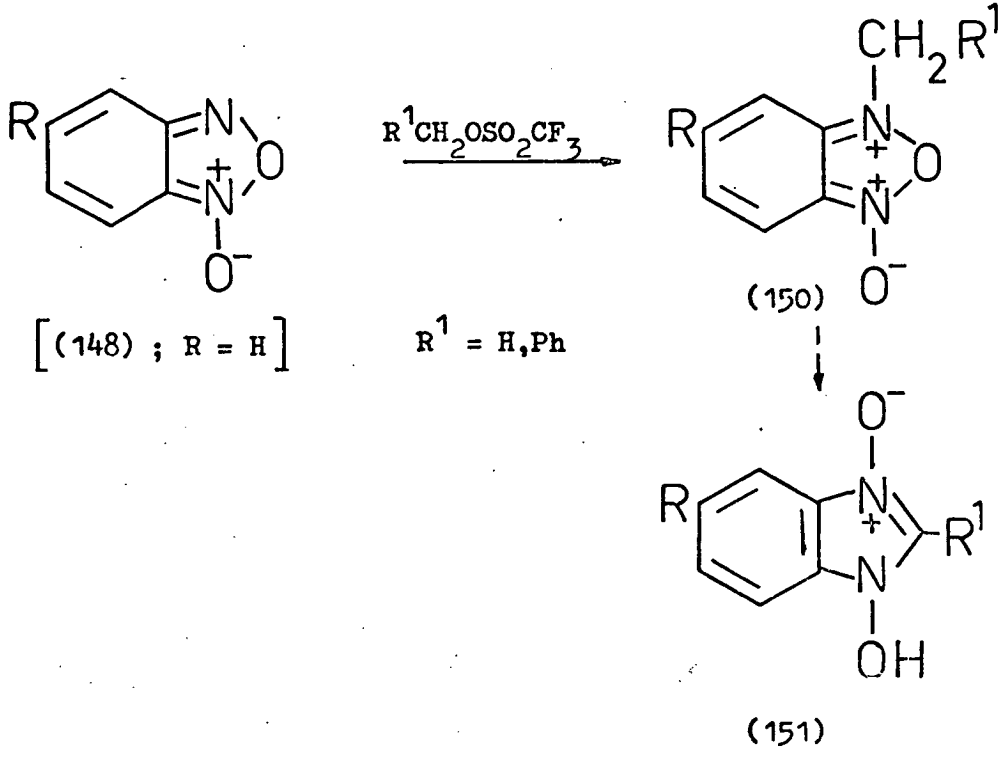
Benzfuroxans (148) have been shown to condense with formaldehyde in the presence of alkali to give good yields of 1,3-dihydroxy-benzimidazolin-2-ones (149).[60] Benzfuroxans (148) containing a



(148) (149)

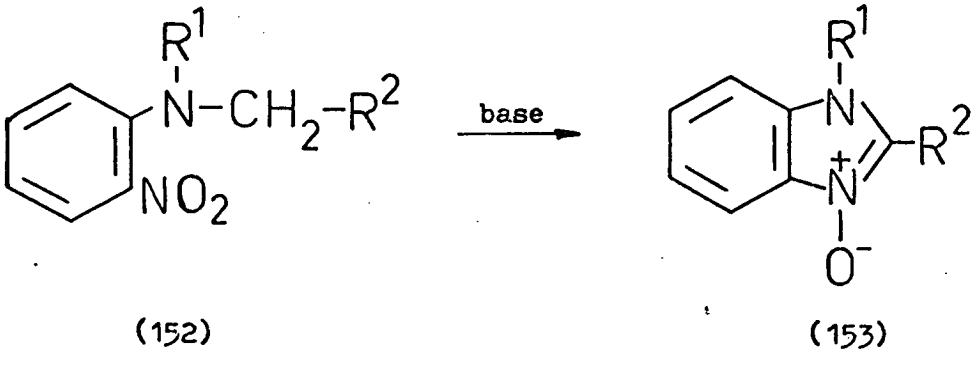
variety of substituents (R = H, Cl, CH_3, CH_3O, COOH and $CONH_2$) in the ring have been used in this reaction.

Alkylation of benzfuroxan [(148) ; R = H] using methyl and benzyl trifluoromethanesulphonate gives the quaternary intermediates (150) which undergo rearrangement to give the 1-hydroxybenzimidazole 3-oxides (151) [61] (scheme 28).



scheme 28

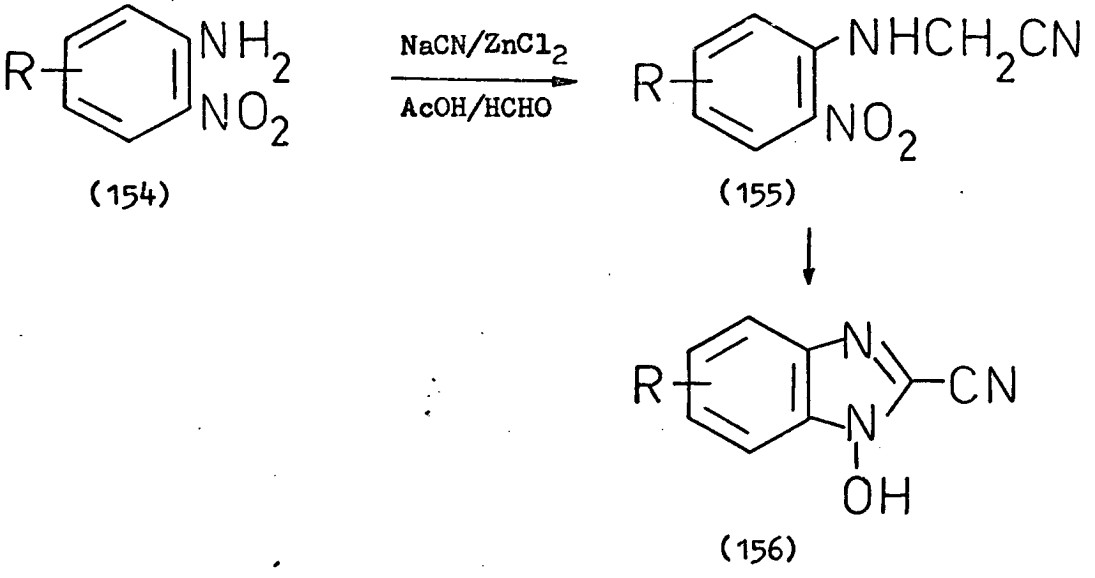
It was of interest to study extensions of the base catalysed aldol-type cyclisations (152→153) since only the cases where



R^2 = Ph (cf. 132→136) (scheme 25) and R^2 = COPh (cf. 139→140) have

been studied previously. The synthesis of compounds (152) in which $R^1 \neq H$ is of particular interest since cyclisation of these compounds would yield benzimidazole N-oxides (153) in which tautomerism is not possible and which are not readily available by other methods. In addition, it would be interesting to study the reactivity of the benzimidazole N-oxides (153).

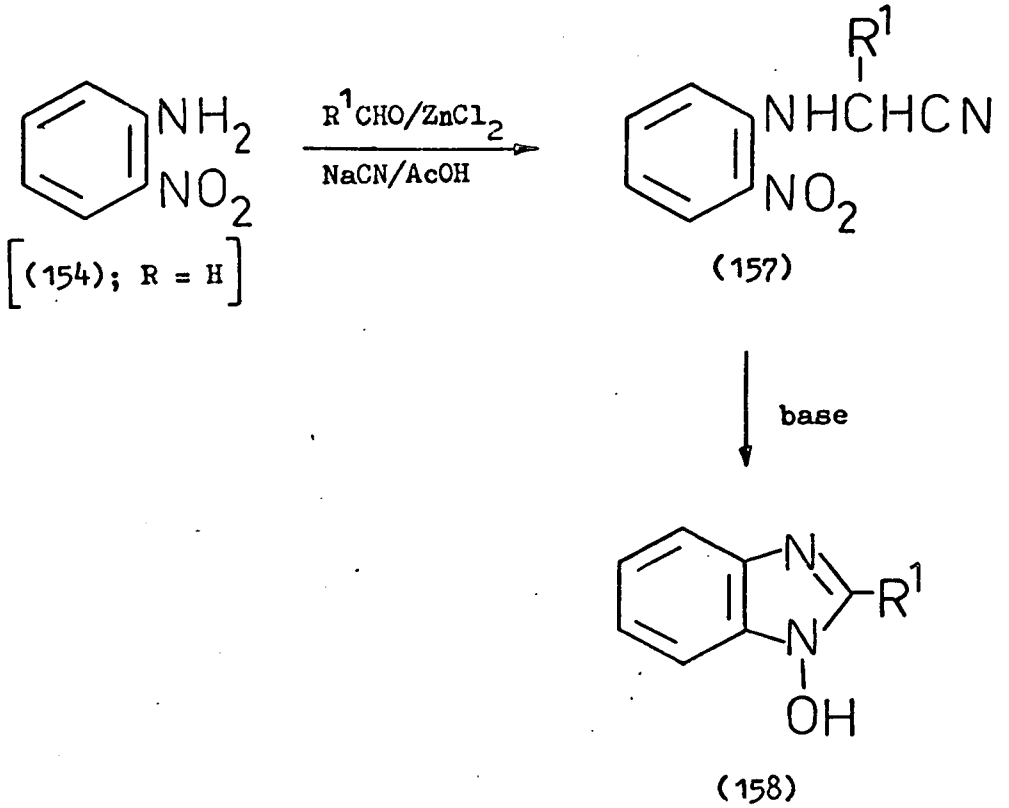
It had been reported[62] that cyanomethylation of 2-nitroaniline [(154); R = H] using sodium cyanide, formaldehyde, and zinc chloride in glacial acetic acid gave 2-nitroanilinoacetonitrile [(155); R = H]. Base catalysed cyclisation of the cyanomethyl compound [(155); R = H] had been shown[63] to give the N-hydroxybenzimidazole [(156); R = H] (scheme 29) (cf. scheme 25). The



(154) (155) (156)

scheme 29

initial object of the research work in this section was to extend the cyanomethylation reaction (154→155) (scheme 29) to cases where substituents were present in the ring (R = chloro, methyl and methoxyl) and then to attempt the cyclisation of these cyanomethyl

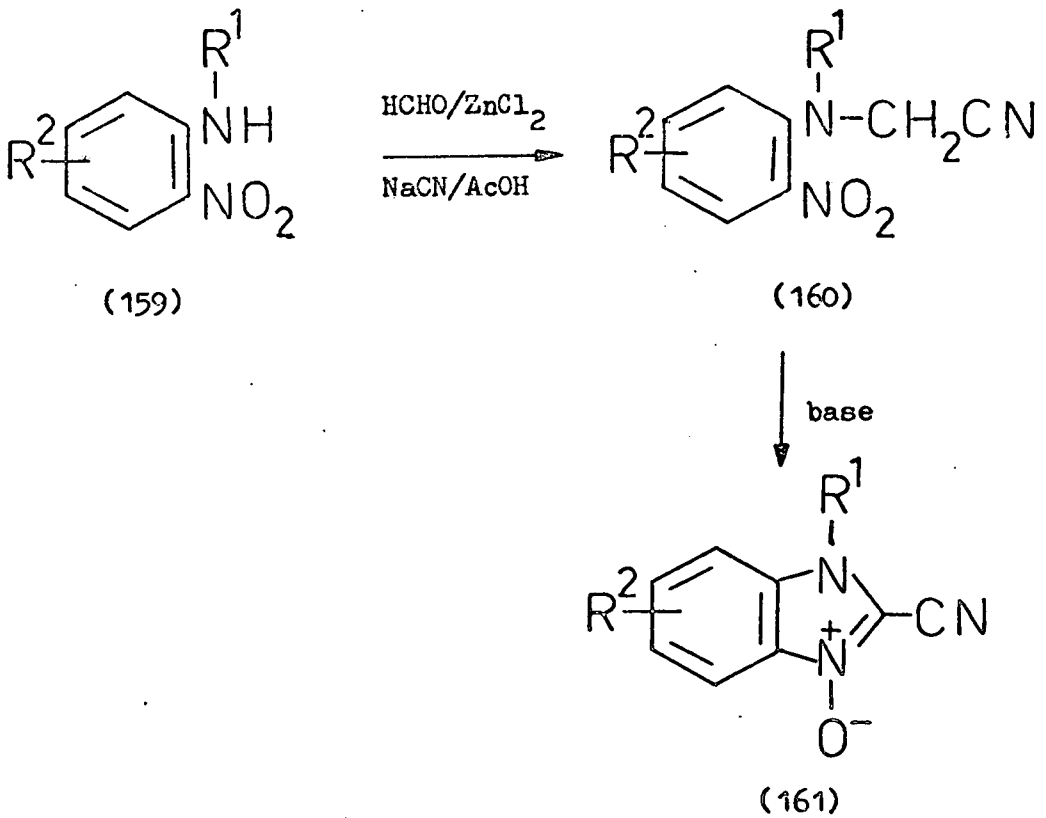


[(154); R = H]

(157)

(158)

scheme 30



(159)

(160)

(161)

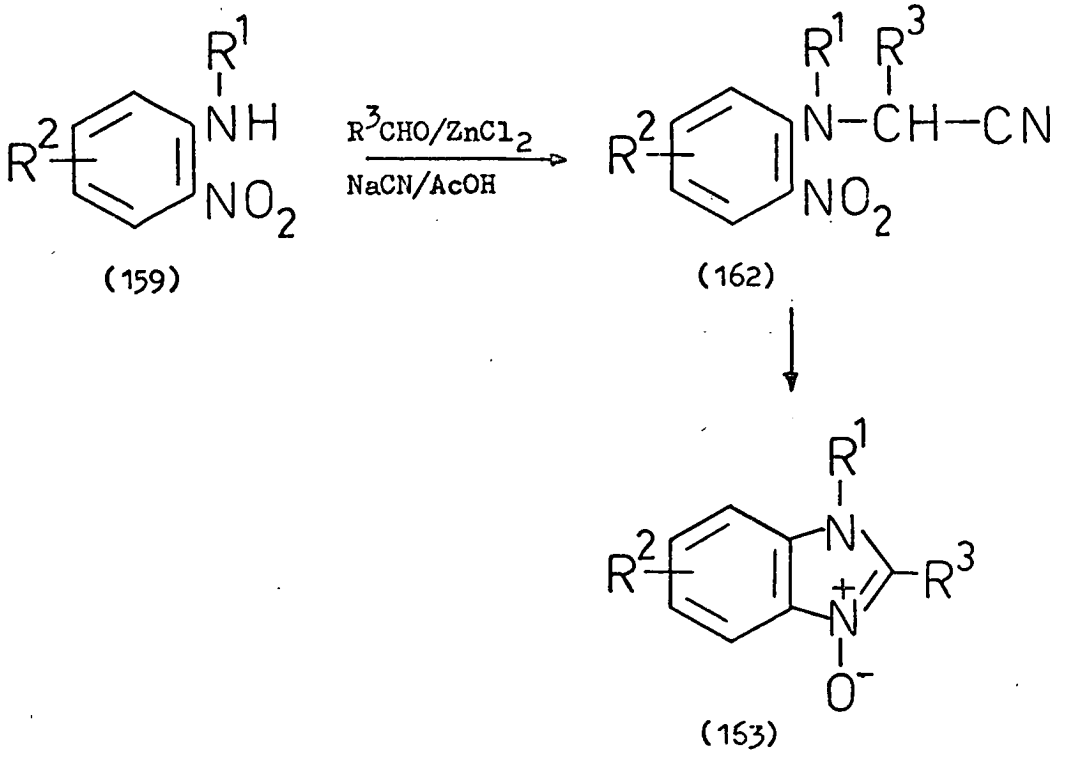
scheme 31

compounds (155) to N-hydroxybenzimidazoles (156).

The next extension of the work was to replace the formaldehyde in the cyanomethylation process (154→155) by other aldehydes (scheme 30) in order to synthesise the α-substituted nitriles (157) which might then be cyclised to the N-hydroxybenzimidazoles (158).

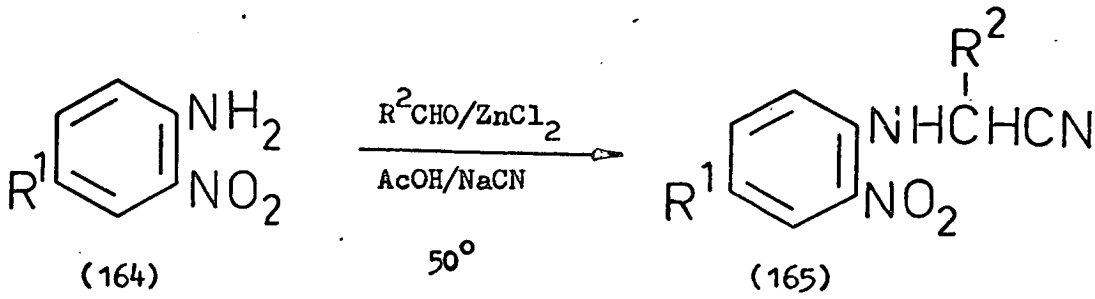
By carrying out the cyanomethylation of N-substituted 2-nitroanilines (159) (scheme 31) the nitriles (158) could be prepared and would then be expected to cyclise to the 2-cyanobenzimidazole N-oxides (161).

Finally, reacting the N-substituted 2-nitroanilines (159) (scheme 32) with zinc chloride, sodium cyanide and aldehydes other than formaldehyde might be expected to give the nitriles (162) capable of cyclisation to the benzimidazole N-oxides (163) (cf. 152→153). This cyclisation is important since it would yield benzimidazole N-oxides (163) in which tautomerism is not possible.



(159) (162) (163)

scheme 32



(164) (165)

	R^1	R^2
(a)	H	H
(b)	Cl	H
(c)	CH_3	H
(d)	CH_3O	H
(e)	H	CH_3
(f)	H	Ph

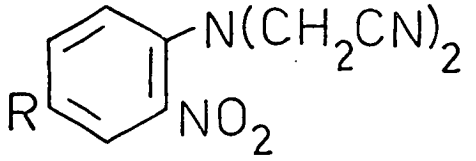
scheme 33

4.2 The Synthesis of 2-Nitroanilinoacetonitriles and Substituted 2-Nitroanilinoacetonitriles

(a) 2-Nitroanilinoacetonitriles

As mentioned above,[62] cyanomethylation of 2-nitroaniline (164a) gives a high yield of 2-nitroanilinoacetonitrile (165a). This cyanomethylation reaction was extended to 2-nitroanilines containing a substituent in the ring. The 2-nitroanilinoacetonitriles (165 a and b) (scheme 33) were prepared in high yield by this method. The i.r. spectrum of compound (165a) contained absorption bands at 3450 cm^{-1} and 1520 and 1360-1340 cm^{-1} which are characteristic of an N-H group and a nitro group respectively. The i.r. spectrum of compound (165 b) contained cyano absorption at 2220 cm^{-1} but there was no cyano absorption in the i.r. spectrum of compound (165a). The ^1H n.m.r. spectrum and the analytical data obtained for compound (165b) were fully in accord with the assigned structure.

When an attempt was made to prepare the 4-methyl derivative (165c) by an analogous procedure (scheme 33), the ^1H n.m.r. spectrum of the product obtained showed it to be a 2:1 mixture of N,N-bis(cyanomethyl)-4-methyl-2-nitroaniline (166a) and 4-methyl-2-nitroanilinoacetonitrile (165c). The i.r. spectrum of the mixture



(166)

	R
(a)	CH_3
(b)	CH_3O

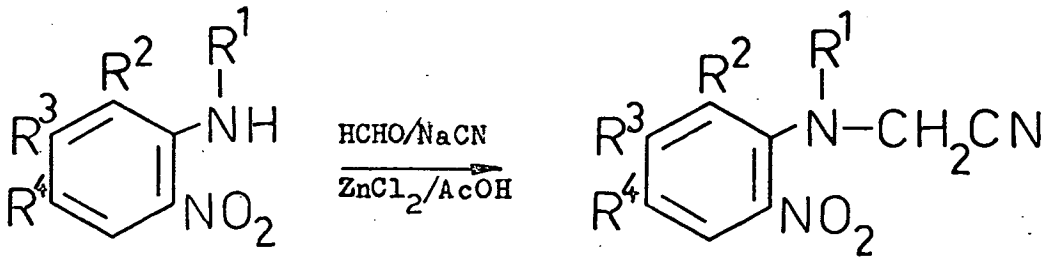
contained an absorption band at 3400 cm^{-1} attributable to the N-H group of compound (165c) and also absorption bands attributable to cyano and nitro groups. The mass spectrum of the product contained peaks corresponding to 230 and 191 mass units attributable to (166a) and (165c) respectively. The mixture crystallised unchanged from organic solvents. The t.l.c. of the mixture in various organic solvents indicated a single component and for this reason the separation of the mixture by column chromatography was not attempted. Consequently, the mixture could not be resolved.

In the case of the 4-methoxy derivative (165d), the product from the cyanomethylation (scheme 33) was again shown to be a mixture by its ^1H n.m.r. spectrum. The mixture was resolved by fractional crystallisation and pure samples of 4-methoxy-2-nitroanilinoacetonitrile (165d) and the dicyano derivative (166b) were obtained and were characterised by their spectroscopic properties and analytical data.

(b) <u>α-Substituted 2-Nitroanilinoacetonitriles</u>

The cyanomethylation reaction (scheme 33) was extended to other aldehydes. Acetaldehyde and benzaldehyde were found to react with 2-nitroaniline to give high yields of the corresponding nitriles (165 e and f) which were characterised by their i.r. and ^1H n.m.r. spectra and their analytical data. The absorption band due to the cyano group was variable in intensity in the compounds (165) and was absent from the i.r. spectrum of compound (165f).

It should be noted that although the cyanomethylation reaction (scheme 33) was originally carried out using a reaction time of 6 h, it was subsequently found that a reaction time of 0.5-1.0 h was sufficient for complete reaction.



(167) (168)

	R^1	R^2	R^3	R^4
(a)	CH_3	H	H	H
(b)	Ph	H	H	H
(c)	$PhCH_2$	H	H	H
(d)	$PhCH_2$	H	CH_3	H
(e)	$PhCH_2$	H	H	Cl
(f)	$PhCH_2$	H	Cl	H
(g)	$PhCH_2$	Cl	H	H

scheme 34

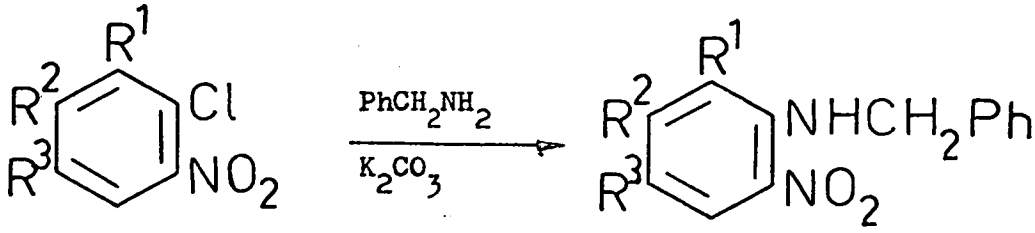
(c) N-Substituted 2-Nitroanilinoacetonitriles

The cyanomethylation reaction was also successfully extended to secondary amines (scheme 34) and good yields of the N-substituted 2-nitroanilinoacetonitriles (168) were obtained. As mentioned previously (scheme 31) it was anticipated that the compounds (168) might cyclise to benzimidazole N-oxides [cf. (161)].

The N-methyl derivative (168a) was obtained in high yield as a yellow oil for which satisfactory spectroscopic data was obtained. No attempt was made to have the oil (168a) analysed and it was purified by chromatography and used directly in subsequent reactions. In the synthesis of the N-methyl compound (168a) reduction of the reaction time from 6 h to 1 h resulted in a quantitative yield of the N-methyl compound (168a) which was pure enough (as demonstrated by its ^{1}H n.m.r. spectrum) to use directly in the subsequent cyclisation. When the time of the reaction leading to (168a) was prolonged to 6 h N-methyl-2-nitroaniline (167a) was also isolated. Since none of the amine (167a) could be detected using the shorter reaction time, formation of the amine (167a) is probably due to decyanomethylation of (168a).

Cyanomethylation of 2-nitrodiphenylamine (167b) using a reaction time of 6 h gave the N-phenyl derivative (168b) (scheme 34) in good yield. An unidentified orange solid which gave analytical and mass spectral data consistent with the formula $C_{29}H_{22}N_6O_4$ was also isolated in this reaction. Its i.r. spectrum contained absorptions characteristic of a nitro group but lacked cyano absorption. Its ^{1}H n.m.r. spectrum showed only aromatic and methylene absorptions.

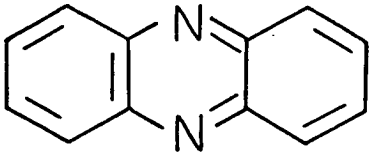
The preparation of (168b) also gave a trace of phenazine (169)



(170)	R^1	R^2	R^3	(167)
(a)	H	H	H	(c)
(b)	H	CH_3	H	(d)
(c)	H	H	Cl	(e)
(d)	H	Cl	H	(f)
(e)	Cl	H	H	(g)

scheme 35

as a by-product. The stability of 2-nitrodiphenylamine to treatment with zinc chloride in the presence of acetic acid excludes the possibility of its direct cyclisation to phenazine. Consequently,

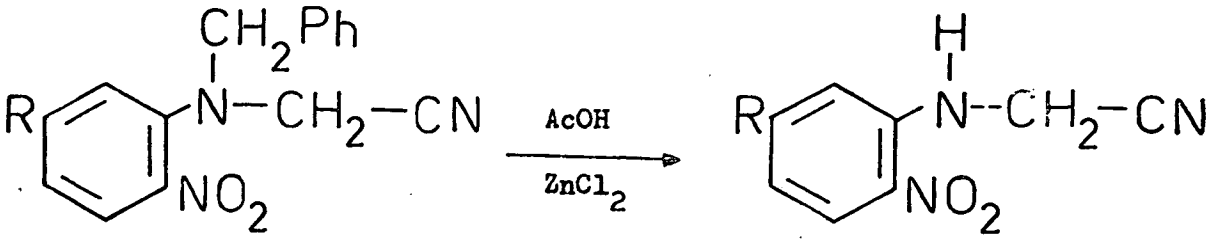


(169)

the mode of formation of the latter product is not clear.

The cyanomethylation reaction was extended to N-benzyl derivatives. The N-benzyl-2-nitroanilines (167 c-g) (scheme 35) were obtained in good yield by the reaction of the corresponding 2-nitrochlorobenzene derivatives (170 a-e) with benzylamine using potassium carbonate as the catalyst.[64] The i.r. spectra of the compounds (167 c-g) all contained absorption bands at approximately 3400 cm^{-1} and 1520 and 1360 cm^{-1} characteristic of N-H and nitro-groups respectively. The melting points of the compounds (167 c, e and f) were in accord with the literature values.[64,65] In accord with preferential replacement of the more reactive chlorine ortho to the nitro-group, the products from the dichloronitrobenzenes (170 c-e) are formulated as (167 e-g). The structure of the compound (167d) was confirmed by its analysis and its ^1H n.m.r. spectrum.

In the case of the dichloro compound (170e) an excess of benzylamine was used in the reaction and the product (167g) which was obtained was contaminated with benzaldehyde. Once the benzaldehyde had been removed by treatment with saturated aqueous sodium bisulphite, the compound (167g) was obtained as a red oil whose spectroscopic properties were fully in accord with the assigned



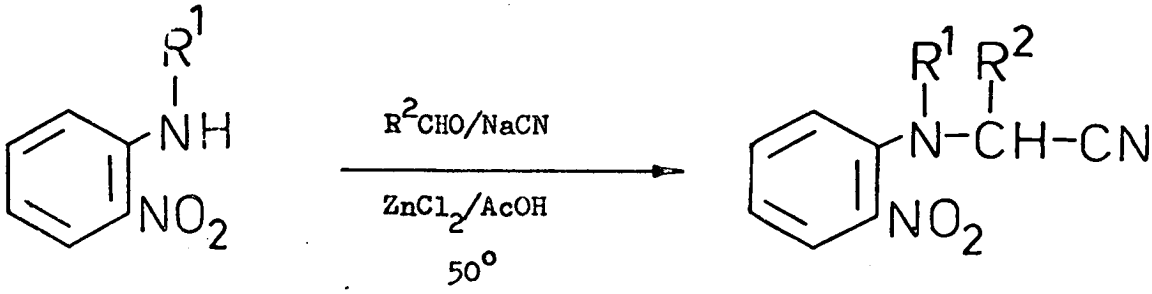
(168)	R	(165)	R
(c)	H	(a)	H
(d)	CH_3	(g)	CH_3
(f)	Cl	(h)	Cl

scheme 36

structure. No attempt was made to have the compound (167g) analysed and it was subsequently used in the cyanomethylation reaction without further purification.

Cyanomethylation of the N-benzyl compound (167c) (scheme 34) using a reaction time of 6 h gave a good yield of the nitrile (168c) as a yellow oil. Satisfactory spectral data was obtained for compound (168c) but no attempt was made to have the oil analysed. Moderate yields of the N-unsubstituted nitrile (165a) and benzyl acetate were also obtained in this reaction and were characterised by comparison with authentic samples. The formation of the nitrile (165a) and benzyl acetate can be rationalised by zinc chloride catalysed debenzylation of the N-benzyl derivative (168c) (scheme 36). The acid catalysed dealkylation of N-substituted o-nitroanilines is a well known process.[66] Although the debenzylation of (168 d and f) is disadvantageous in that it gives rise to a mixture of products it nevertheless provides a route to the otherwise inaccessible 2-nitroanilinoacetonitriles (165 g and h). A trace of N-benzyl-2-nitroaniline (167c) was also isolated in the preparation of the nitrile (168c). The presence of (167c) in the reaction mixture could be due to incomplete reaction or to decyanomethylation of (168c) in a process analogous to that shown in scheme 36.

N-Benzyl-5-chloro-2-nitroaniline (167f) also underwent cyanomethylation to give a moderate yield of the N-benzyl derivative (168f) and low yields of the corresponding debenzylated product (165h) (scheme 36) and benzyl acetate. The spectroscopic properties and analysis of the nitrile (165h) were fully in accord with the assigned structure. A low yield of a compound assigned the structure (171) was also obtained as a by-product in the preparation

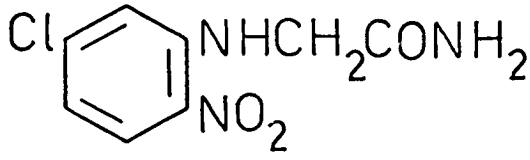


(167)	R^1
(a)	CH_3
(b)	Ph
(c)	$PhCH_2$

(172)	R^1	R^2
(a)	CH_3	Ph
(b)	Ph	CH_3
(c)	$PhCH_2$	Ph

scheme 37

of the nitrile (168f). In accord with the amide structure (171)



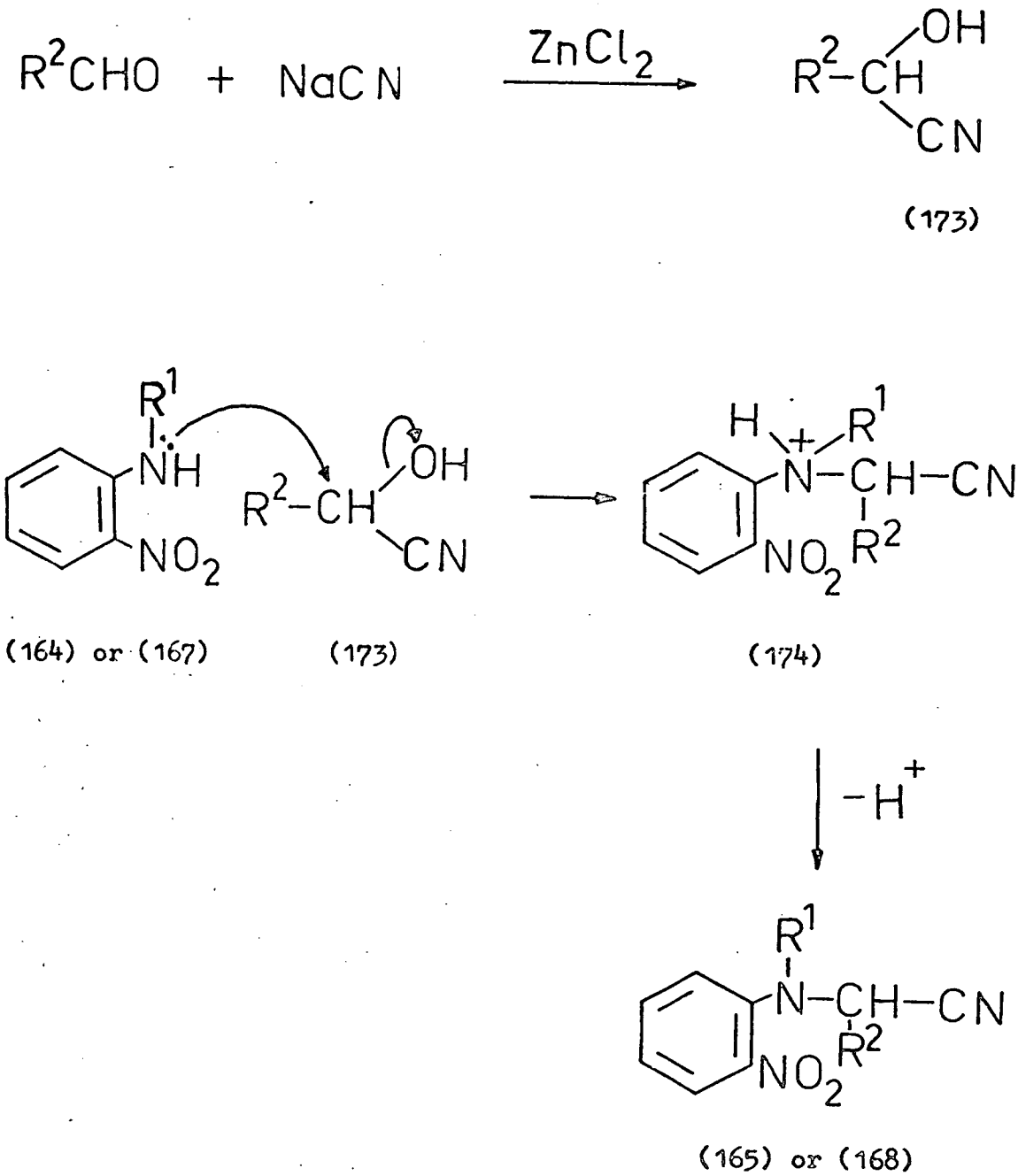
(171)

the by-product showed i.r. amino absorption at 3425 and 3175 cm^{-1} and carbonyl absorption at 1680 cm^{-1} characteristic of a primary amide group as well as absorption due to a nitro-group. The by-product also gave mass spectral and analytical data consistent with the structure (171). The amide (171) is probably formed in the reaction by hydrolysis of the corresponding nitrile (165h).

It was found that in the cyanomethylation of compounds (167 d, e and g) (scheme 34) reducing the reaction time to 20-30 min minimised debenzylation of the products and gave optimum yields of the N-benzyl derivatives (168 d, e and g). In the case of the 4- and 6-chloro derivatives (168 e and g) a trace of benzyl acetate was obtained using a reaction time of 30 min but no products corresponding to debenzylation of (168 e and g) were isolated from the reactions. However, even using a reaction time as short as 20 min, the major product in the cyanomethylation of (167d) was the 5-methyl-N-benzyl derivative (168d), accompanied by a low yield of the nitrile (165g) (scheme 36) demonstrating the facility of debenzylation in this case.

(d) α, N-Disubstituted 2-Nitroanilinoacetonitriles

Attempts to react the secondary amines (167 a-c) with acetaldehyde or benzaldehyde and sodium cyanide in the presence of zinc chloride to give products with the structures (172 a-c) (scheme 37) were


R2CHO + NaCN
ZnCl2
OH
R2–CH
CN
(173)
R1
NH
NO2
R2–CH
OH
CN
(164) or (167)
(173)
H
+
R1
N–CH–CN
NO2
R2
(174)
-H+
R1
N–CH–CN
NO2
R2
(165) or (168)

scheme 38

unsuccessful. When the amines (167 a and c) were treated with benzaldehyde and sodium cyanide in the presence of zinc chloride at 50°, the only compounds isolated in good yield were the starting amines (167 a and c). Increasing the temperature to 100° in the reaction of (167c) with benzaldehyde and sodium cyanide in the presence of zinc chloride resulted in some decomposition and the formation of a low yield of benzyl acetate and starting amine (167c). Substantial quantities of brown intractable gums were also obtained under these forcing conditions and no product corresponding to the disubstituted acetonitrile (172c) was obtained.

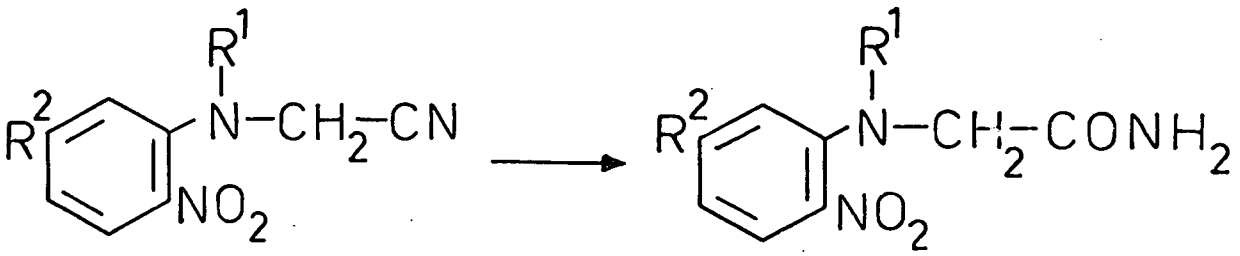
When 2-nitrodiphenylamine (167b) was treated with acetaldehyde and sodium cyanide in the presence of zinc chloride at 50° (scheme 37), the compound isolated from the reaction was shown by t.l.c. to be starting amine (167b), contaminated with acetaldehyde. No product corresponding to (172b) was isolated.

The failure of the reaction of the amines (167 a-c) with acetaldehyde and benzaldehyde was unfortunate since the products (172 a-c) would be expected to cyclise to benzimidazole N-oxides as discussed previously (page 130, scheme 32).

Discussion of the Reaction Mechanism of Cyanomethylation

A mechanism which explains the cyanomethylation of the amines (164) and (167) to give the cyano compounds (165) and (168) is outlined in scheme 38. Nucleophilic attack by sodium cyanide on the aldehyde gives the cyanohydrin (173) which in turn undergoes nucleophilic attack by the amine (164) or (167) with elimination of water to give the observed cyano compounds (165) or (168).

In the case of the unsubstituted amines (164) the yields of the



Nitrile	R^1	R^2	Amide
(165a)	H	H	(175)
(165h)	H	Cl	(171)
(168a)	CH_3	H	(176)
(168c)	$PhCH_2$	H	(177)

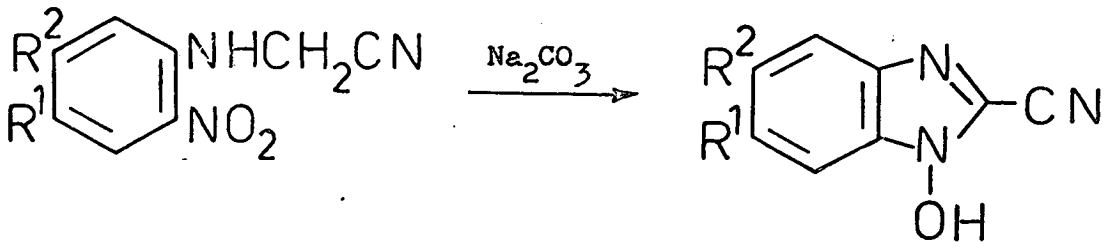
scheme 39

nitriles (165) are high and were not dependent on the reactivity of the aldehyde used in the reaction. Thus acetaldehyde which is a less reactive aldehyde than formaldehyde gave a high yield of the nitrile (165e) (scheme 33). This suggests that the factor governing the reactivity in the process (164→165) (scheme 33) is the basicity or nucleophilicity of the amine group in the amine (164).

The fact that the secondary amines (167 a-c) react with formaldehyde and sodium cyanide in the presence of zinc chloride (scheme 34) but do not react with acetaldehyde or benzaldehyde under similar conditions (scheme 37) suggests that the reactivity of the aldehyde used in the reaction is critical. It is also possible that steric hindrance is preventing the reaction (167→172) (scheme 37) from taking place.

Hydrolysis of 2-Nitroanilinoacetonitriles

Hydrolysis of the 2-nitroanilinoacetonitriles (165 a and h) and (168 a and c) using polyphosphoric acid gave good yields of the corresponding amides (scheme 39). The amide (171) obtained in this reaction was identical with a sample obtained previously (page 135). The spectroscopic properties of the amides (171) and (175-177) were fully consistent with the assigned structures. In the reaction of the N-benzyl nitrile (168c) with polyphosphoric acid some debenzylation took place and a moderate yield of the amide (175) was obtained as well as a low yield of the N-benzyl derivative (177). The spectroscopic properties of the amide (177) were fully in accord with assigned structure but there was insufficient material to obtain satisfactory analytical data for the compound.



(165)	R^1	R^2	(178)
(a)	H	H	(a)
(b)	Cl	H	(b)
(d)	CH_3O	H	(c)
(g)	H	CH_3	(d)

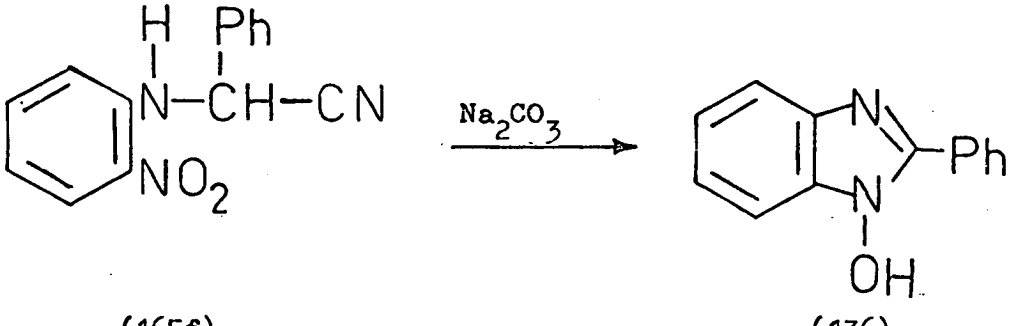
scheme 40

4.3 The Base-catalysed Cyclisation of 2-Nitroanilinoacetonitriles

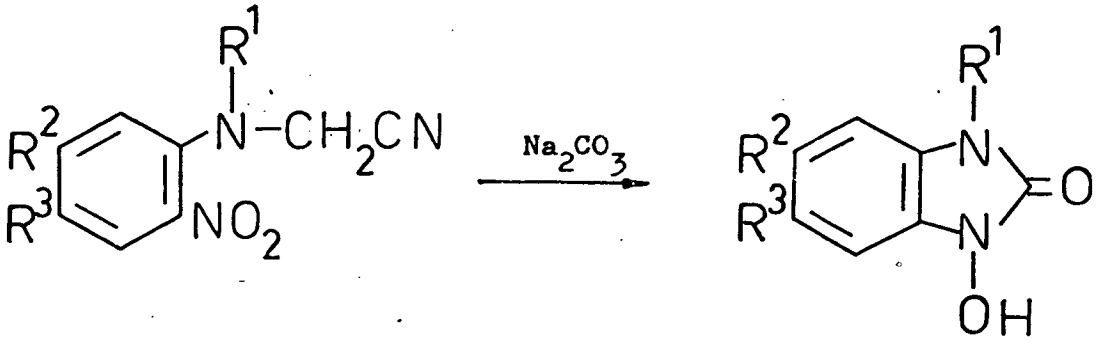
The 2-nitroanilinoacetonitriles (165 a, b, d and g) underwent base-catalysed cyclisation when heated with aqueous methanolic sodium carbonate giving high yields of the corresponding N-hydroxybenzimidazoles (178 a-d) (scheme 40). These reactions are analagous to previously reported cyclisations[55] [cf. (139)→(140), page 125]. The N-hydroxybenzimidazoles (178 a-d) gave analytical and spectroscopic data consistent with their assigned structures. Their i.r. spectra all contained broad absorption bands at ca. 2500 cm^{-1} characteristic of a hydroxyl group and weak absorption bands at ca. 2300 cm^{-1} attributable to a cyano group.

The compound (178a) was identical with a sample prepared previously[63] and was reduced by sodium dithionite to a product whose m.p. and spectral properties were consistent with its being the known[67] compound 2-cyanobenzimidazole. The i.r. spectrum of the reduced compound contained a broad absorption band at 3100-2600 cm^{-1} and a weak absorption band at 2330 cm^{-1} which are characteristic of an N-H group and a cyano group respectively. The mass spectrum showed the molecular weight to be 143 corresponding to 2-cyanobenzimidazole.

The phenylacetonitrile derivative (165f) underwent base-catalysed cyclisation to give a low yield of 1-hydroxy-2-phenylbenzimidazole (136) which was characterised by comparison with an authentic sample.



(165f) (136)

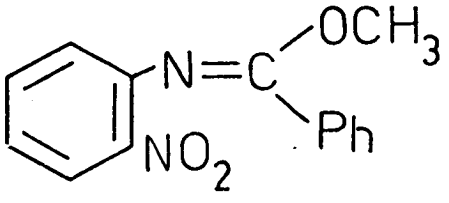


(168) (181)

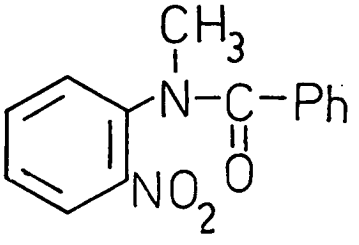
	R^1	R^2	R^3
(a)	CH_3	H	H
(b)	Ph	H	H
(c)	$PhCH_2$	H	H
(d)	$PhCH_2$	CH_3	H
(e)	$PhCH_2$	H	Cl
(f)	$PhCH_2$	Cl	H

scheme 41

Chromatography of the non-acidic material from this reaction gave a low yield of a compound whose analytical and mass spectral data were consistent with the formula $C_{14}H_{12}N_2O_3$. Possible structures for this product are (179) and (180). The i.r. spectrum contained



(179)



(180)

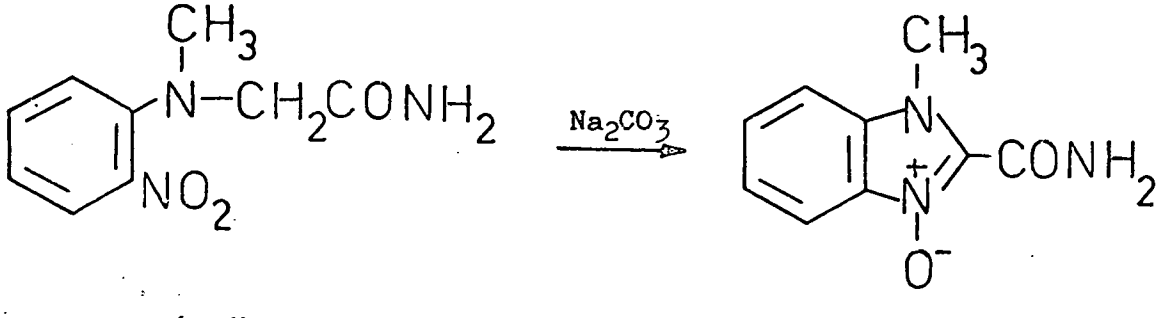
absorption bands characteristic of a nitro group and an absroption band at 1680-1660 cm^{-1} attributable to an azomethine (C = N) or carbonyl group. The ^1H n.m.r. spectrum showed the presence of nine aromatic protons and contained a singlet at τ 6.01 corresponding to an N-methyl or O-methyl group. The melting point of the unidentified compound is 84° while that of the benzanilide derivative (180) is 81°.[68] Thus compound (180) cannot be excluded on the basis of its literature melting point since the melting points are similar.

The attempted cyclisation of the propionitrile derivative (165e) using sodium carbonate as the catalyst gave brown intractable gums from which no products were identified. The failure of the nitrile (165e) to cyclise could be due to the reduction in the acidity of the methine group as a result of methyl substitution.

Cyclisation of the N-substituted 2-nitroanilinoacetonitriles (168 a-e) gave good yields of the corresponding N-hydroxy-benzimidazolinones (181 a-e) (scheme 41) for which satisfactory analytical and spectral data were obtained. Their i.r. spectra

contained broad absorption bands at ca. 2700 cm^{-1} and at ca. 1700 cm^{-1} which are characteristic of a hydrogen-bonded hydroxyl group and a carbonyl group respectively. The presence of the N-hydroxyl group in the compounds (181 a-e) was indicated by their enhanced acidity and by the production of a dark green colour with ferric chloride in ethanol.[43] The melting point of the compound (181a) was slightly lower than that reported by Kano[17] for 1-hydroxy-3-methylbenzimidazolin-2-one (181a).

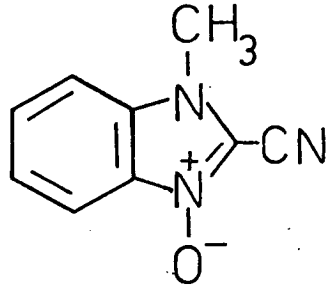
In the preparation of the compounds (181 a-e) some non-acidic gums were obtained and in the case of the N-methyl derivative (181a), the gum was chromatographed. Low yields of N-methyl-2-nitroaniline (167a) and N-methyl-2-nitroanilinoacetonitrile (168a) were obtained. A low yield of the amide (176) was also obtained. The amide (176) is probably formed in the reaction by hydrolysis of the corresponding nitrile (168a). This mode of formation is supported by the fact that the nitrile (168a) is readily hydrolysed to the amide (176) by polyphosphoric acid (scheme 39, page 138). The non-acidic gum from the preparation of the N-methyl derivative (181a) also afforded a low yield of a product corresponding to the N-oxide (182). The spectroscopic properties of the product (182) were fully in accord with the assigned structure and the melting point was consistent with the reported[17] value for 1-methylbenzimidazole-2-carboxamide



(176) (182)

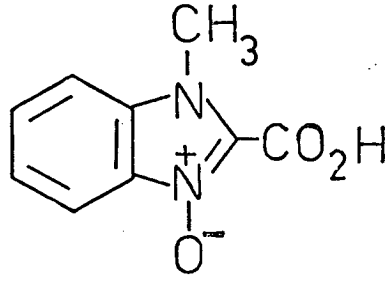
scheme 42

3-N-oxide (182). The N-oxide (182) is probably formed either by base-catalysed cyclisation of the amide (176) (scheme 42) or by hydrolysis of the nitrile (183) the presumed intermediate in the



(183)

cyclisation of the nitrile (168a) to the hydroxamic acid (181a). The former mode of formation is supported by the fact that the amide (176) was cyclised to the N-oxide (182) in low yield by heating in aqueous methanolic sodium carbonate. The last reaction also gave a low yield of an acidic product whose spectral properties were consistent with the carboxylic acid structure (184). The i.r. spectrum contained broad absorption bands at ca. 2700 and 1700 cm^{-1}



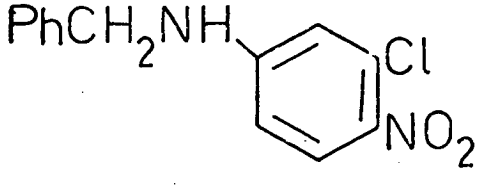
(184)

attributable to a carboxyl group. The ^1H n.m.r. and mass spectra were also fully in accord with the assigned structure (184). The literature[17] melting point of the N-oxide (184) however did not correspond with the melting point of the compound (184) obtained in

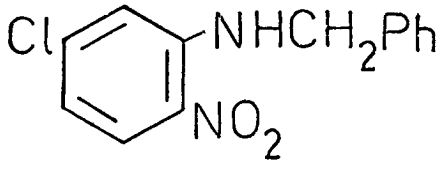
the present work and unfortunately there was insufficient material to fully characterise compound (184) by analysis. An attempt to cyclise the amide (176) using sodium acetate as the catalyst was unsuccessful probably because the acetate ion is not a strong enough base.

No attempt was made to separate the multicomponent gums also obtained in the syntheses of the benzimidazolinones (181 b-e).

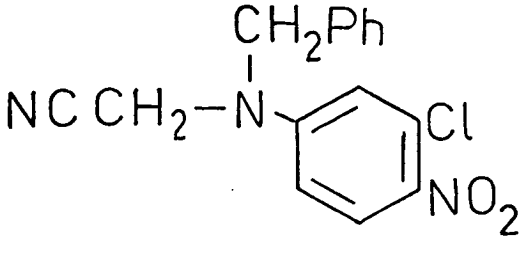
The attempt to cyclise the nitrile (168f) using aqueous methanolic sodium carbonate was unsuccessful and no product corresponding to the N-hydroxybenzimidazolinone (181f) was obtained. One possibility for the failure of the last reaction was that in the reaction of the dichloro compound (170d) with benzylamine (scheme 35) (page 134) displacement of the 4-chloro group rather than the 2-chloro group had occurred to give (185) rather than (167f) and hence by cyanomethylation (186) and not (168f). However, this



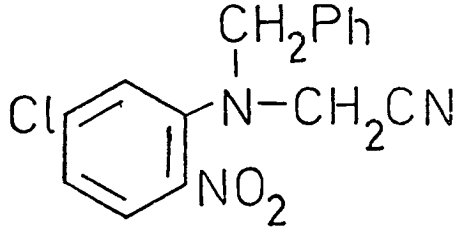
(185)



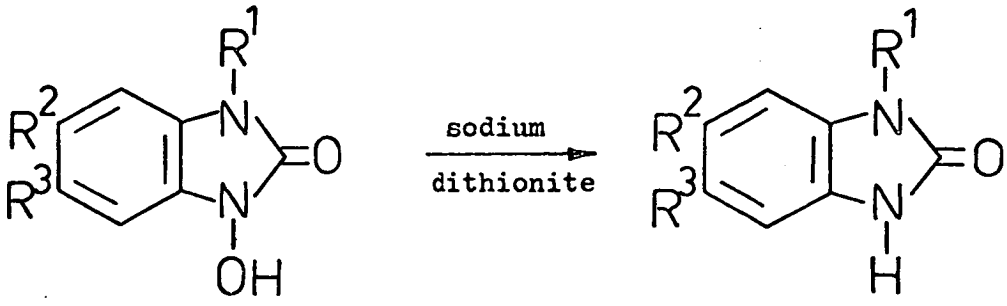
(167f)



(186)



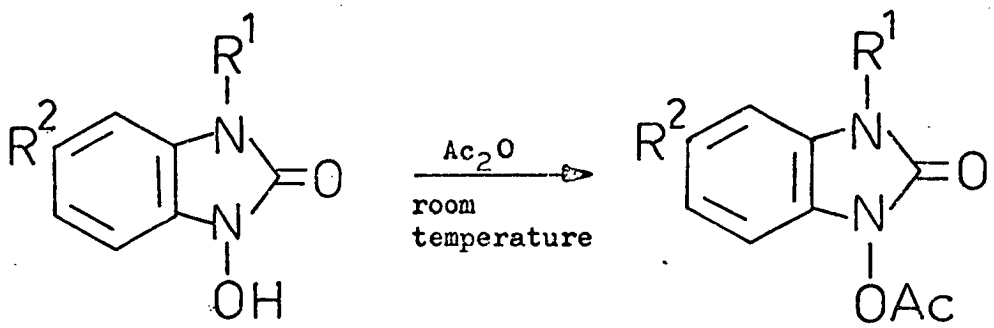
(168f)



(181) (188)

	R^1	R^2	R^3
(a)	CH_3	H	H
(b)	Ph	H	H
(c)	$PhCH_2$	H	H
(d)	$PhCH_2$	CH_3	H
(e)	$PhCH_2$	H	Cl

scheme 43

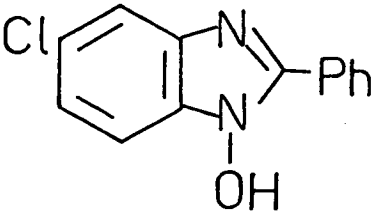


(181) (190)

	R^1	R^2	
(a)	CH_3	H	(a)
(c)	$PhCH_2$	H	(b)
(d)	$PhCH_2$	CH_3	(c)

scheme 44

reason for the failure of the aforementioned cyclisation is excluded by the fact that in accord with its assigned structure the amine (167f) undergoes cyclisation on treatment with methanolic sodium hydroxide[53] to give the known N-hydroxybenzimidazole (187). The

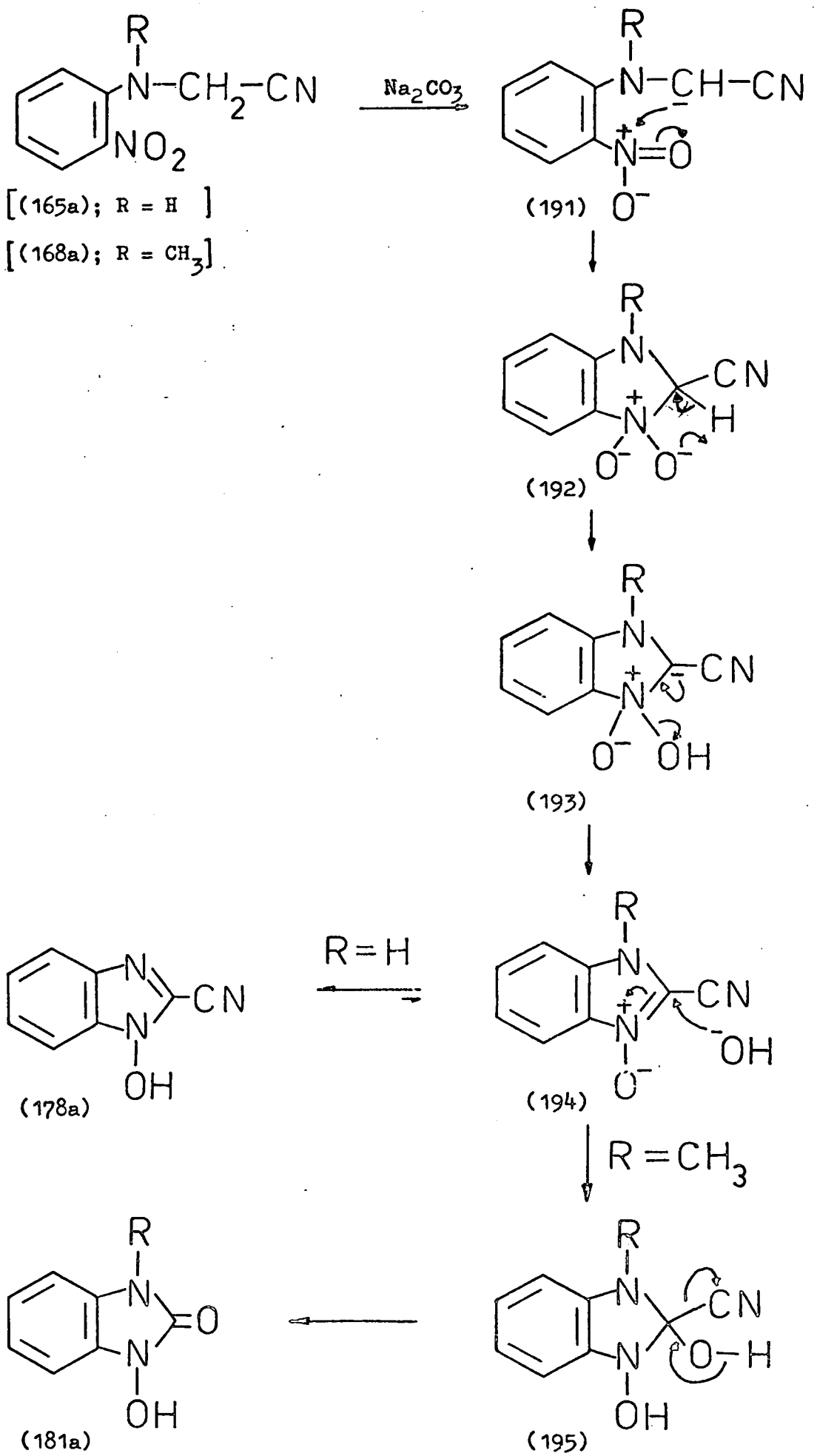


(187)

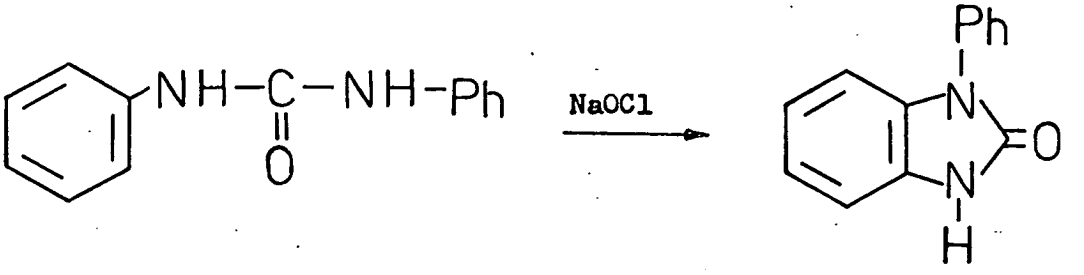
melting point of this product was somewhat higher than the literature value[69] but its properties were fully in accord with the structure (187).

Proof of Structure of N-Hydroxybenzimidazolinones

The N-hydroxybenzimidazolinones (181 a-e) gave high yields of the corresponding benzimidazolinones (188 a-e) (scheme 43) on reduction with sodium dithionite. Satisfactory spectral data were obtained for the benzimidazolinones (188 a-e) and the melting points of (188a-c and e) were in accord with the literature values.[70-73] Compound (188d) is a new compound for which satisfactory analytical data was obtained. Thus reduction of the N-hydroxybenzimidazolinones (181) to known benzimidazolinones (188) establishes unambiguously the structures of the N-hydroxy compounds (188). The structure of compound (188b) was confirmed by comparison with an authentic sample prepared by the cyclisation of diphenylurea (189) using sodium hypochlorite as described by Rosnati[72] (189→188b).


R
N–CH2–CN
NO2
Na2CO3
[(165a); R = H]
[(168a); R = CH3]
(191)
(192)
(193)
CN
H
OH
(178a)
R=H
(194)
R=CH3
(181a)
(195)

scheme 45



(189) (188b)

The reaction of the N-hydroxybenzimidazolinones (181 a, c and d) with acetic anhydride at room temperature provided further evidence for the structure of the N-hydroxy compounds (181). Thus mild acetylation of the N-hydroxy compounds (181 a, c and d) gave high yields of the N-acetoxy derivatives (190 a-c) (scheme 44) which is characteristic of the reaction of an N-hydroxy compound with acetic anhydride. The i.r. spectra of compounds (190 a-c) showed absorption bands in their i.r. spectra characteristic of an N-acetoxy group.[43]

The N-phenyl compound (181b) reacted with acetic anhydride at room temperature to give a gum and an N-acetoxy derivative was not isolated in this case.

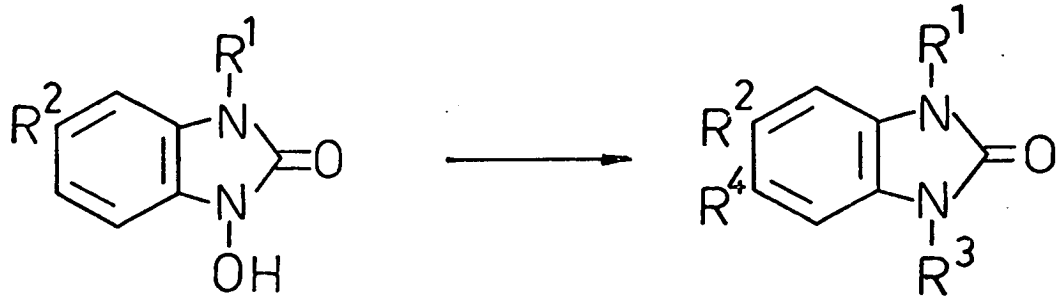
Mechanisms of the Base-Catalysed Cyclisations of 2-Nitroanilino-acetonitrile Derivatives

The base-catalysed cyclisation of the 2-nitroanilino-acetonitriles (165 a-d) and (168) can be rationalised by the mechanisms summarised in scheme 45 for the N-unsubstituted acetonitrile (165a) and the N-methyl derivative (168a) respectively. The first step in these cyclisations is abstraction of a proton from the active methylene group in (165a) or (168a) to give the carbanions (191). Nucleophilic attack on the nitro group by the negative centre in (191) gives the intermediate (192) which by a proton shift generates a negative charge at the 2-position to give the intermediate

(193). Elimination of hydroxide ion from (193) then gives the corresponding 2-cyanobenzimidazole N-oxide (194) which in the case where R = H, is tautomeric with the N-hydroxybenzimidazole (178a) isolated in the reaction (cf. scheme 40). In the case where R = CH_3, the N-oxide (194) is not isolated but undergoes addition of water to give the intermediate (195) which by elimination of hydrogen cyanide gives the N-hydroxybenzimidazolinone (181a) observed as product (cf. scheme 41). The intermediate formation of the nitrile (194) is supported by the isolation of the corresponding amide (181) (scheme 42) as a by product in the cyclisation. The steps [(194)→(195)→(178a)] are further supported by the reported[17] base-catalysed conversion of the N-oxide [(194); R = CH_3] into the N-hydroxybenzimidazolinone (181a).

The cyclisation of the α-phenyl derivative (165f) to the N-hydroxybenzimidazole (136) supports the mechanism suggested for the cyanide-catalysed formation[54] of the N-hydroxybenzimidazole (136) from N-benzylidene-2-nitroaniline (137) (page 124).

The cyclisation of the amide (176) to the N-oxide (182) (scheme 42, page 141) can be rationalised by a mechanism analogous to that outlined in scheme 45 for the nitrile (168a).



(181) (196)

	R^1	R^2
(a)	CH_3	H
(b)	Ph	H
(c)	$PhCH_2$	H
(d)	$PhCH_2$	CH_3

	R^1	R^2	R^3	R^4
(a)	CH_3	AcO	H	H
(b)	$PhCH_2$	AcO	H	H
(c)	CH_3	Cl	Ac	H
(d)	Ph	Cl	Ac	H
(e)	$PhCH_2$	Cl	Ac	H
(f)	$PhCH_2$	CH_3	Ac	Cl
(g)	$PhCH_2$	CH_3	H	Cl
(h)	CH_3	Br	Ac	H
(i)	Ph	Br	Ac	H
(j)	$PhCH_2$	Br	Ac	H
(k)	Ph	Br	H	H
(l)	$PhCH_2$	Br	H	H
(m)	$PhCH_2$	H	$PhCO_2$	H
(n)	Ph	$PhCO_2$	H	H
(o)	$PhCH_2$	CH_3	H	AcO
(p)	CH_3	Cl	H	H
(q)	CH_3	Br	H	H
(r)	CH_3	Pr^nCO_2	H	H

scheme 46

4.4 Reactions of 1-Hydroxybenzimidazolin-2-ones

(i) Acetic Anhydride

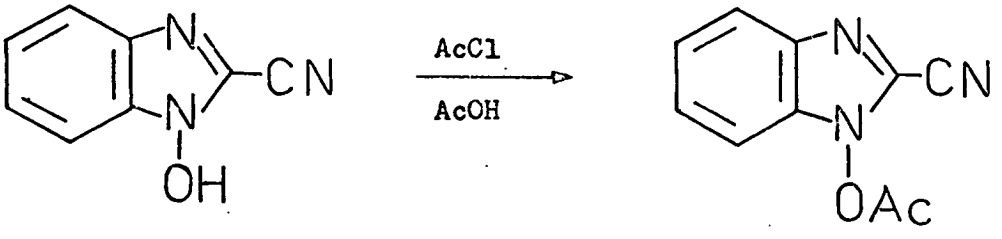
In contrast to their behaviour at room temperature, reaction of the N-hydroxybenzimidazolinones (181 a-d) with hot acetic anhydride caused an exothermic reaction to take place giving tarry material from which it was difficult to isolate any products. The compounds (181 b and d) both gave brown intractable gums while in the case of the N-benzyl compound (181c) a moderate yield of the 5-acetoxy derivative (196b) was isolated (scheme 46). The acetoxy group in (196b) was shown to be in the 5-position by the characteristic splitting pattern of the aromatic protons (H-4, H-6 and H-7) in its ^{1}H n.m.r. spectrum. In accord with the C-acetoxy structure (196b) the i.r. spectrum of the product showed characteristic carbonyl absorption at 1755 cm^{-1}. The mass spectrum and analytical data obtained for compound (196b) were consistent with the assigned structure. It should be noted however that the evidence cited does not exclude the possibility that the acetoxy group is in the 6-position.

The reaction of the N-methyl compound (181a) with hot acetic anhydride produced a low yield of the 5-acetoxy compound (196a) for which satisfactory spectroscopic and analytical data were obtained. The last reaction also produced an unidentified solid which on attempted crystallisation gave a gelatinous precipitate. The presence of an acetoxy group in this product was shown by broad absorption in its i.r. spectrum at 1740 cm^{-1}. The ^{1}H n.m.r. spectrum of this product contained aromatic protons, a multiplet in the N-methyl region and a doublet corresponding to an acetoxy group. When one considers the structure of the starting material (181a) it is

difficult to see how a pure compound containing a multiplet in the N-methyl region could be obtained by reaction with acetic anhydride. One possibility is that the multiplicity in the N-methyl region is due to the polymeric nature of the product. That multiplicity in the N-methyl region cannot be due to coupling with the acetoxy group is demonstrated by the fact that irradiation at the signals due to the acetoxy group did not affect the multiplicity in the N-methyl region.

When the reaction of the N-methyl compound (181a) with acetic anhydride was carried out in the presence of concentrated sulphuric acid, a violent exothermic reaction took place and a brown intractable gum was obtained.

In contrast to the ease with which the N-hydroxybenzimidazolinones (181) reacted with hot acetic anhydride, 2-cyano-1-hydroxybenzimidazole (178a) was recovered in almost quantitative yield after being heated under reflux in acetic anhydride for 3 h. A trace of a compound containing an N-acetoxy group and a cyano group (as shown by the characteristic absorption bands at 1815 cm^{-1} and 2270 cm^{-1} in the i.r. spectrum) was obtained in this reaction. This compound was also obtained in high yield when the benzimidazole (178a) was heated under reflux with acetyl chloride in glacial acetic acid, and is assigned the structure (197). However on attempted crystallisation from

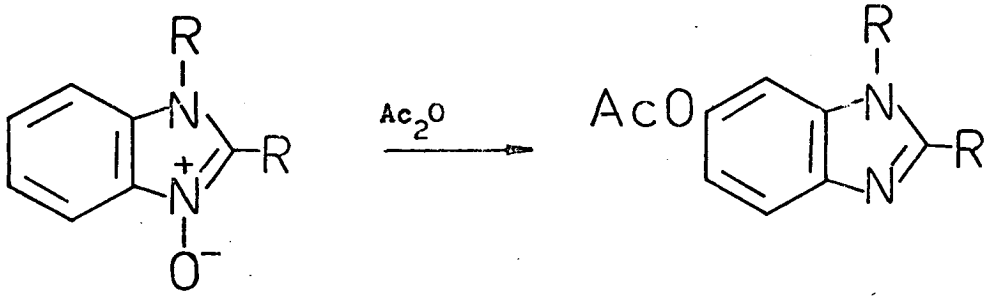


(178a) (197)

ethanol, the N-acetoxy derivative (197) was hydrolysed back to the starting N-hydroxybenzimidazole (178a) and consequently it could not be fully characterised by analysis.

The mechanism of the reaction of the benzimidazolinones (181) with acetic anhydride will be discussed later (page 160).

Substitution in the 5-position of an N-oxygenated benzimidazole by acetic anhydride has been observed before. Thus 2,3-disubstituted benzimidazole 1-oxides (35) react with acetic anhydride to give 5-acetoxybenzimidazoles[17] (36) as mentioned in chapter one (page 9).



(35) (36)

(ii) Acetyl Chloride

The N-hydroxybenzimidazolinones (181 a-c) reacted with acetyl chloride in glacial acetic acid to give high yields of products whose spectral properties and analytical data were fully in accord with the 5-chloro-N-acetyl structures (196 c-e) (scheme 46). The products (196 c-e) showed i.r. carbonyl absorptions at ca. 1740 cm^{-1} and ^1H n.m.r. absorption at τ 7.23-7.28 consistent with the presence of an N-acetyl group. The 5-position for the chloro substituent is in accord with the splitting pattern of the aromatic proton resonances in the ^1H n.m.r. spectra of the compounds (196 c-e) which is characteristic of a 1,2,4-trisubstituted benzene derivative.

The reaction of the compound (181d) with acetyl chloride in

glacial acetic acid gave a product which is assigned the structure (196f). Its i.r. spectrum contained a carbonyl band at 1740 cm^{-1} and its ^1H n.m.r. spectrum contained methyl absorption at τ 7.23 confirming the presence of an N-acetyl group. The chloro substituent in (196f) was shown to be in the 6-position by the lack of splitting in the ^1H n.m.r. signals due to the H-4 and H-7 aromatic protons. The mass spectrum of the product was also in accord with structure (196f). However, on crystallisation from ethanol-glacial acetic acid for analysis, the compound (196f) was deacetylated to the benzimidazolinone (196g) (scheme 46) for which satisfactory mass spectral and analytical data were obtained.

The mechanism of the reactions of compounds (181 a-d) (scheme 46) with acetyl chloride will be discussed later.

(iii) Acetyl Bromide

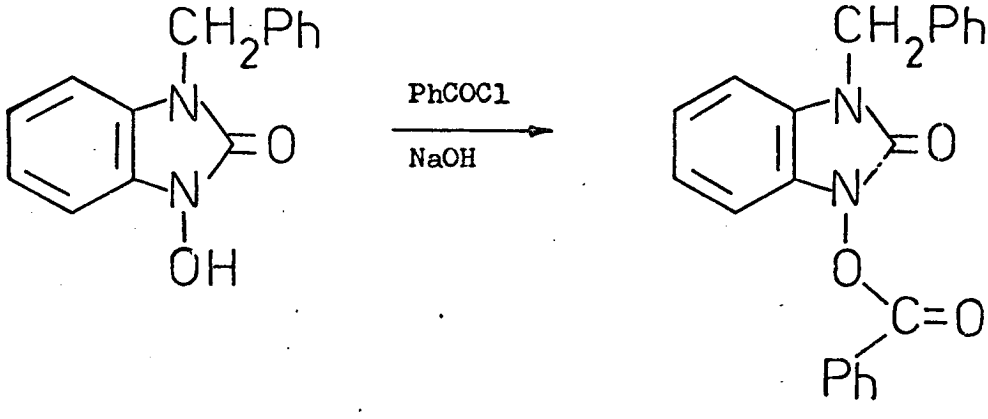
The N-hydroxybenzimidazolinone (181a) reacted with acetyl bromide in glacial acetic acid to give a moderate yield of the 5-bromo derivative (196h) (scheme 46). The structure of this product was verified as for the 5-chloro analogue (196c).

The compounds (181 b and c) reacted with acetyl bromide to give products which were shown to be mixtures by their ^1H n.m.r. spectra and by t.l.c. Attempts to resolve these mixtures by crystallisation were unsuccessful. In the case of the N-phenyl compound (181b) the mixture was acetylated using acetic anhydride but the product from the acetylation was still a mixture as shown by its ^1H n.m.r. spectrum and t.l.c. The mixtures in these reactions could arise by reduction of the N-hydroxy compounds (181 b and c) to the benzimidazolinones (188 b and c) respectively. Hydrogen bromide arising from reaction of acetyl bromide with glacial acetic acid

could effect this reduction. It is also possible that the compounds (196 i and j) (scheme 46) are being formed in the reaction and are then undergoing deacetylation to the compounds (196 k and l) (scheme 46) respectively. Thus the complexity of the acetyl bromide reaction compared with the acetyl chloride reaction may be due to the fact that hydrogen bromide is a better reducing agent than hydrogen chloride.

(iv) Benzoyl Chloride

The N-benzyl compound (181c) reacted with benzoyl chloride in the presence of aqueous sodium hydroxide in a Schotten-Baumann type of reaction to give a good yield of a product which gave correct analytical data for the benzoyloxy derivative (196m). The presence of the benzoyloxy group in the product (196m) was shown by the

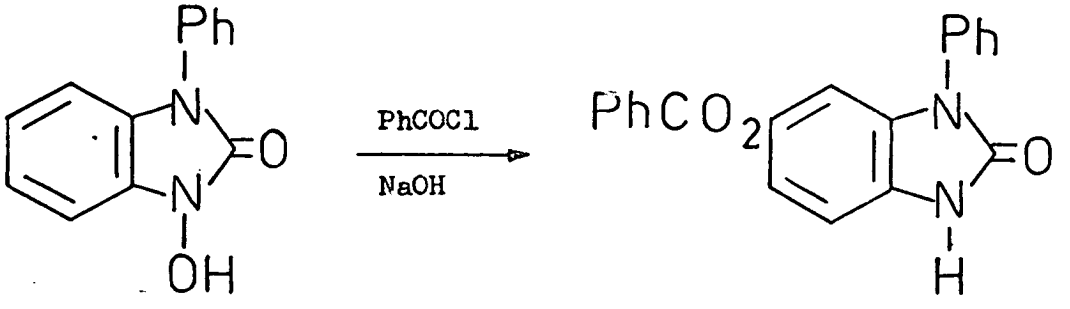


(181c) (196m)

characteristic carbonyl absorption at 1770 cm^{-1} in the i.r. spectrum. This reaction provides further evidence for the presence of the N-hydroxyl group in the compound (181c).

In contrast, the reaction of the N-phenyl compound (181b) with benzoyl chloride in the presence of aqueous sodium hydroxide gave a good yield of a compound which was shown to be the

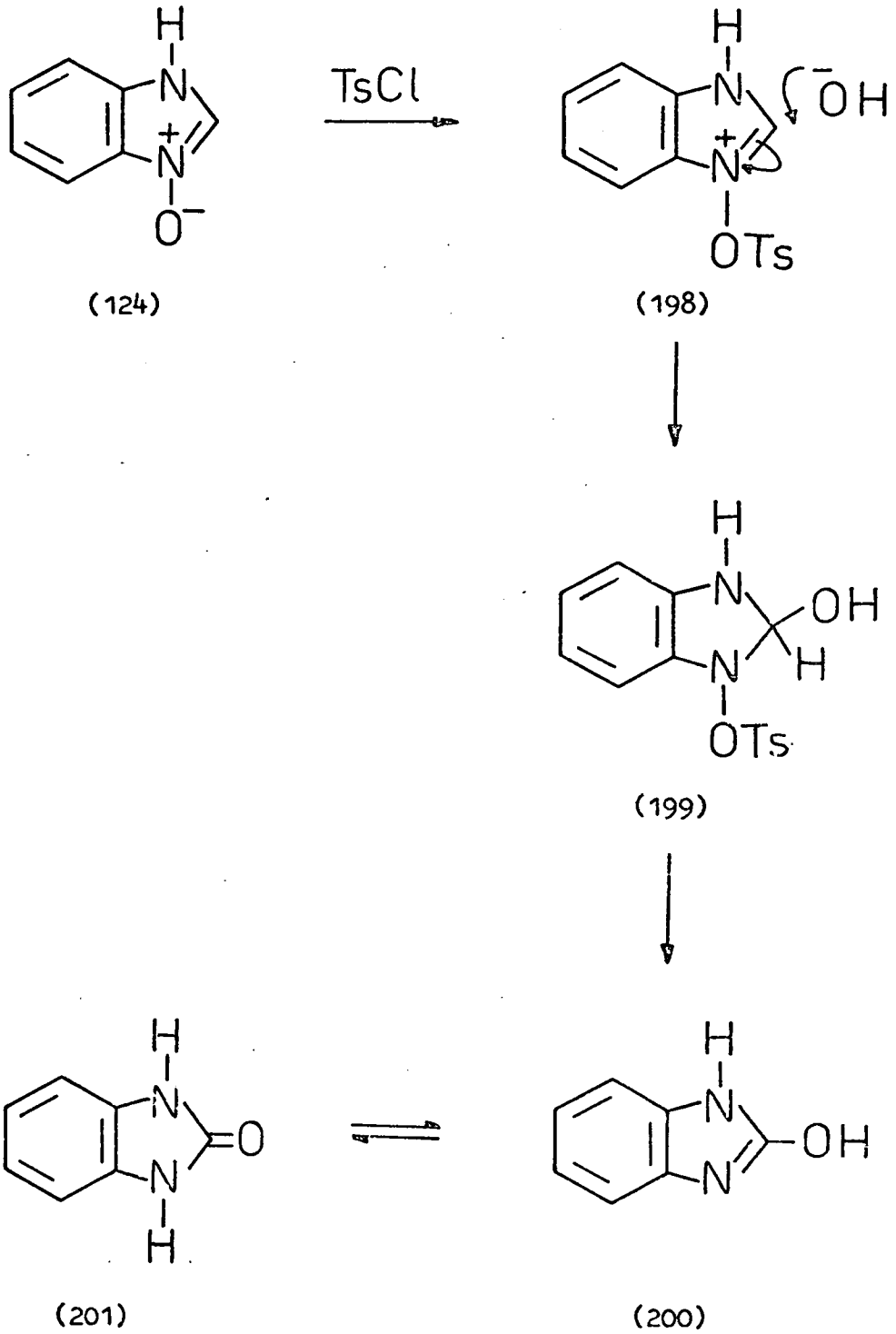
5-benzoyloxy derivative (196n). The presence of the C-benzoyloxy



(181b) (196n)

group in (196n) was shown by the presence of an absorption band at 1720 cm^{-1} in its i.r. spectrum. The ^1H n.m.r. spectrum of the product contained signals which can be assigned to H-4 and H-6 in the structure (196n). The 5-position for the benzoyloxy group is fully consistent with the splitting pattern of the aromatic protons. H-7 which would be ortho-coupled was obscured by the other aromatic protons in the molecule.

The reason for the difference in the products in the reactions of compounds (181 b and c) with benzoyl chloride is probably due to the different work up procedure employed. In the case of the N-benzyl compound (181c) the product was obtained as a solid which was easily isolated to give the N-benzoyloxy derivative (196m). In the case of the N-phenyl compound (181b), the product was obtained as a gummy solid which was heated under reflux in ethanol to remove the excess of benzoyl chloride. It is probable that the initial product in the reaction was an N-benzoyloxy derivative [cf. (196m)] which underwent rearrangement to give the 5-benzoyloxy derivative (196n). The corresponding rearrangements of N-acetoxy derivatives are discussed later.



(124) (198) (199) (201) (200)

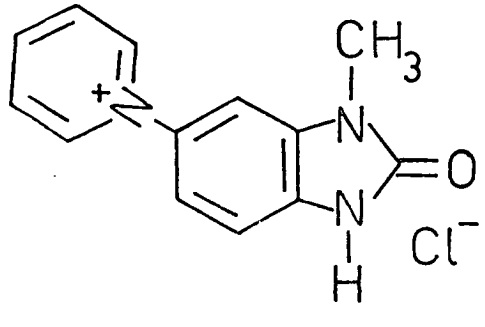
scheme 47

(v) Reactions of 1-Hydroxybenzimidazolin-2-ones in the presence of Toluene-p-sulphonyl Chloride

It has been shown that benzimidazole 1-oxide (124) is converted into the benzimidazolin-2-one (201) when treated with hydroxide ion in the presence of toluene-p-sulphonyl chloride.[50] The reaction probably proceeds by coordination at the N-oxide oxygen atom by tosyl chloride to give the intermediate (198) (scheme 47) which undergoes nucleophilic attack by hydroxide ion giving the intermediate (199). Elimination of toluene-p-sulphonic acid from (199) then gives the 2-hydroxybenzimidazole (200) which is tautomeric with the benzimidazolin-2-one (201).

The reaction of the N-hydroxy compound (181a) with aqueous sodium hydroxide in the presence of toluene-p-sulphonyl chloride gave a brown intractable gum which was shown by t.l.c. to be a multicomponent mixture. Since this last reaction did not give an identifiable product, the reaction of the compound (181a) with toluene-p-sulphonyl chloride in chloroform was carried out. However, this attempted reaction gave a quantitative yield of the starting N-hydroxy compound (181a).

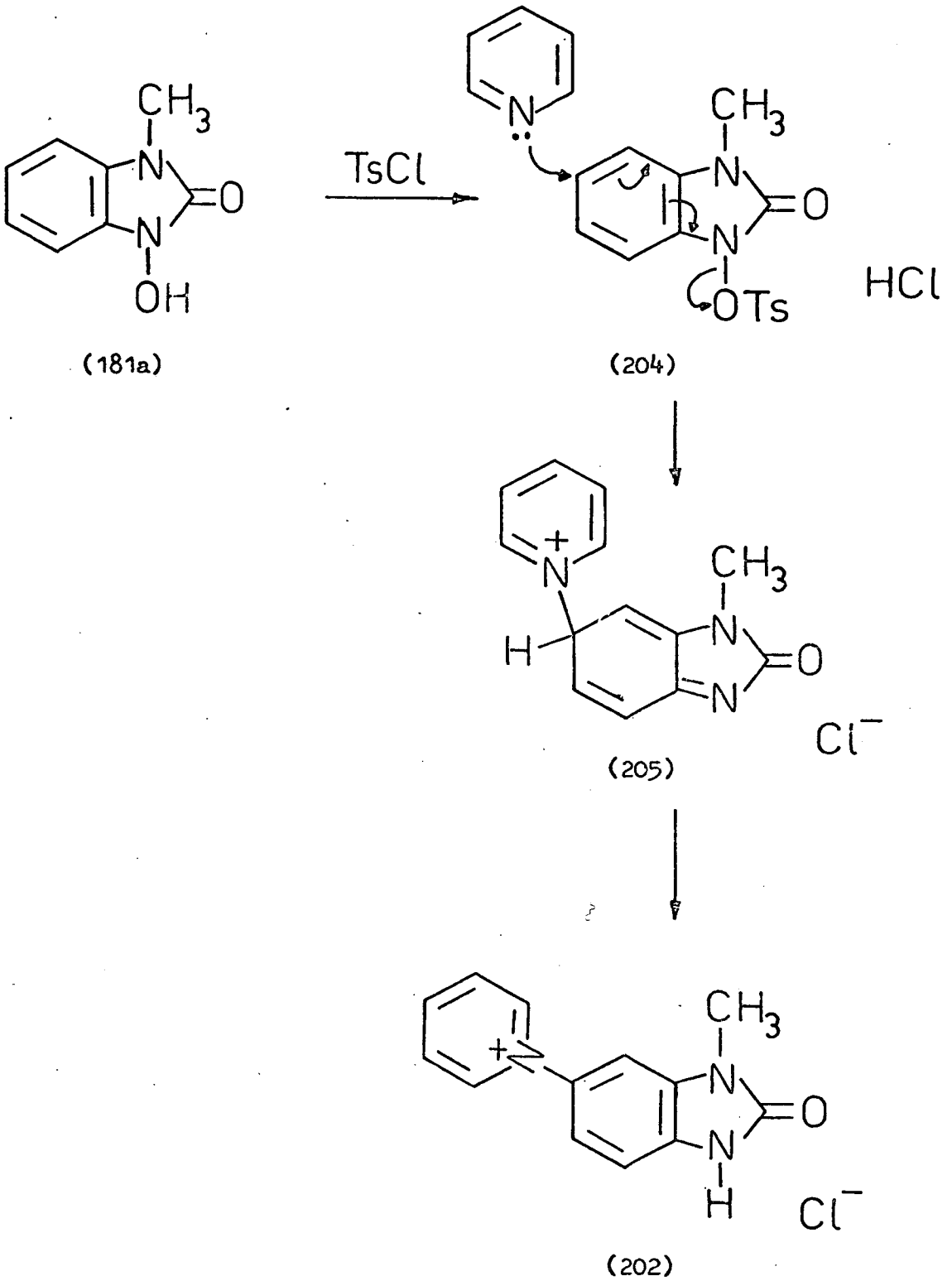
The reaction of the N-hydroxy compound (181a) with toluene-p-sulphonyl chloride in the presence of pyridine gave a good yield of a product which was shown by its spectroscopic properties to be the pyridinium salt (202). The i.r. spectrum contained a broad band at



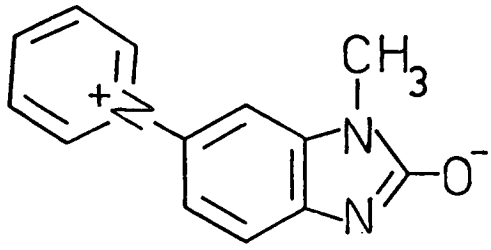
(202)

3350 cm^{-1} characteristic of hydroxyl and amino absorption. The ^1H n.m.r. spectrum of (202) showed the presence of pyridine in the molecule since the integral indicated that there were eight aromatic protons in the compound. The only other signal in the ^1H n.m.r. spectrum was due to the protons of the N-methyl group. The position of the pyridine group in the molecule could not be established unequivocally from the ^1H n.m.r. spectrum due to the complexity of the aromatic region. The position of substitution was taken to be the 5-position by analogy with the orientation of previous substitution reactions [e.g. the reaction of compound (181a) with acetyl chloride and acetyl bromide]. The mass spectrum of the pyridinium salt (202) contained a peak at 226 mass units corresponding to the molecular weight of the cation of the salt (202). The salt could be crystallised from ethanol but it did not give satisfactory analytical data. This is probably due to the mixed character of the counterion of the salt causing differences in its molecular weight. Thus, although the salt is formulated as the chloride (202) it is possible that toluenesulphonate could also function as the counterion leading to a mixture of two possible pyridinium salts. The presence of chloride ion in the salt (202) was shown by the fact that a solution of the salt in water gave a white precipitate when treated with aqueous silver nitrate solution. It was shown that a solution of the benzimidazolinone (188a) in ethanol treated with ethanolic silver nitrate did not give a white precipitate.

The salt (202) also dissolved in aqueous alkali giving a yellow solution from which no colour was extracted into chloroform. This suggests that the salt (202) was possibly forming a zwitterion (203) in alkali and this was not being extracted into the chloroform.


CH3
N
O
N
OH
TsCl
N
CH3
N
O
N
OTs
HCl
(181a)
(204)
N
CH3
H
N
O
N
Cl⁻
(205)
CH3
N
O
N
H
Cl⁻
(202)

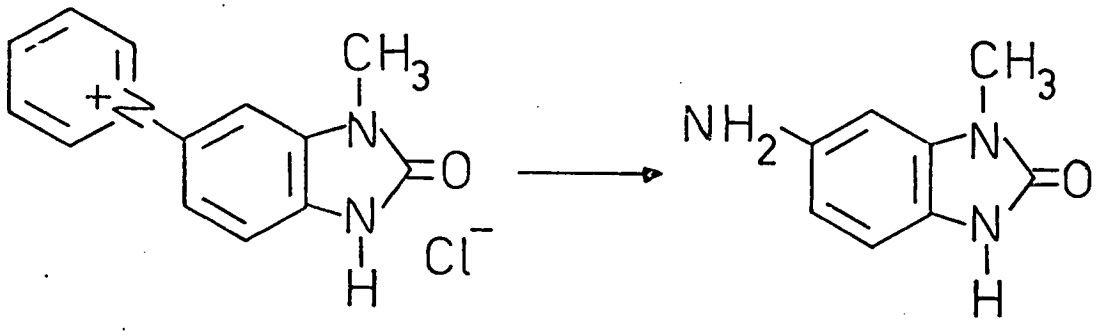
scheme 48



(203)

The formation of the salt (202) can be explained by the mechanism shown in scheme 48. The initial step is reaction of the N-hydroxy compound (181a) with toluene-p-sulphonyl chloride to give the intermediate (204) which undergoes nucleophilic attack at the 5-position by pyridine followed by a proton shift to give the pyridinium salt (205). This process is similar to the reaction of 4-methylquinoline 1-oxide (86) with toluene-p-sulphonyl chloride and pyridine to give the cation (88) as described in chapter one (page 20).

An attempt to cleave the pyridinium salt (202) to the amino compound (206) by heating it under reflux with piperidine in methanol[40]



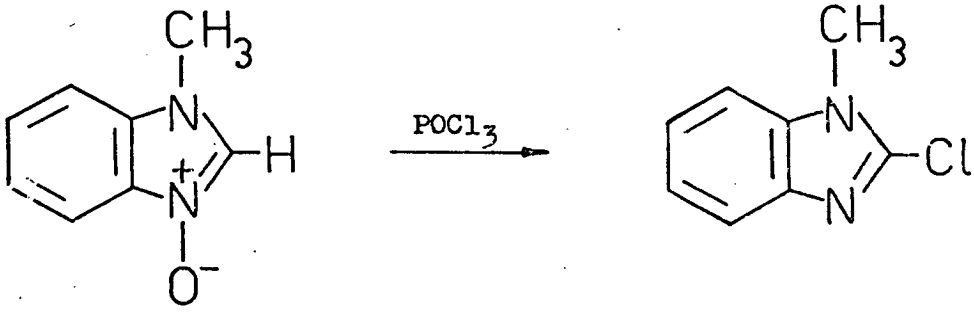
(202) (206)

was unsuccessful. The product from the reaction was an intractable brown gum. The object of this experiment was to degrade the pyridinium salt (202) to a compound whose structure could be more readily established by further degradation to a benzimidazolinone of established structure. This would have established unequivocally the position of the pyridine substituent in the salt (202).

The 5-methyl compound (181d) reacted with pyridine and toluene-p-sulphonyl chloride to give a brown intractable gum from which no definite products could be isolated. Thus, it appears that blocking the 5-position in the hydroxamic acid (181d) alters the course of the reaction.

(vi) Phosphorus Oxychloride

Chlorination of benzimidazole N-oxides has been carried out using phosphorus oxychloride as the chlorinating agent. Thus 3-methylbenzimidazole 1-oxide (207) gives the 2-chlorobenzimidazole (208) when treated with phosphorus oxychloride.[70] The attempted reaction of 1-hydroxy-3-methylbenzimidazolin-2-one (181a) with



(207) (208)

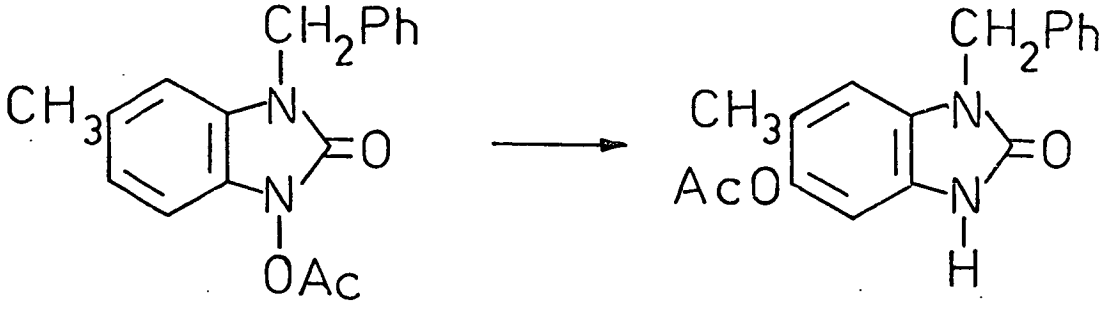
phosphorus oxychloride in chloroform gave an almost quantitative yield of the starting material (181a) and triethylphosphate. This

indicates that the phosphorus oxychloride is being converted into triethylphosphate by the ethanol present in the chloroform and thus no chlorination is taking place. The reaction of (181a) with phosphorus oxychloride was repeated using 1,2-dichloroethane as the solvent and in this case the product was a gum from which no identifiable material could be obtained on trituration.

4.5 Reactions of 1-Acetoxy-3-substituted Benzimidazolin-2-ones

It was found that when the N-acetoxy compounds (190 a and b) were heated under reflux in ethanol, good yields of the corresponding 5-acetoxy derivatives (196 a and b) were obtained. These products were identical with the acetoxy compounds obtained in the reactions of the N-hydroxy compounds (181 a and c) with hot acetic anhydride.

The effect of having a substituent in the 5-position in these N-acetoxybenzimidazolinone rearrangements was investigated by heating the 5-methyl compound (190c) in ethanol. In this case the product obtained in moderate yield was shown to be the 6-acetoxy derivative (196o). This product gave analytical data consistent with its being



(190c) (196o)

isomeric with the starting material and showed i.r. carbonyl absorption at 1740 cm^{-1} consistent with the presence of a C-acetoxy

group. The ^1H n.m.r. spectrum of the product (196o) contained a signal assignable to the protons of a C-methyl group indicating that no attack on the 5-methyl group had taken place. The acetoxy group was shown to be in the 6-position by the fact that the ^1H n.m.r. spectrum revealed no observable splitting in the H-4 and H-7 protons. Thus, it appears that when the 5-position is blocked, the most reactive position in the benzimidazolinone (190c) is the 6-position. A similar result was obtained in the reaction of the N-hydroxy compound (181d) with acetyl chloride (page 149).

The N-acetoxy compound (190a) was recovered unchanged after being heated under reflux in benzene for 1 h. Since the boiling points of ethanol and benzene are comparable, it would appear that the less polar nature of benzene with respect to ethanol is causing this difference in reactivity.

On heating under reflux in toluene, the N-acetoxy compound (190a) underwent rearrangement to afford a good yield of the 5-acetoxy derivative (196a) which was characterised by comparison with a sample obtained previously. This reaction also gave a moderate yield of the unidentified polymeric solid obtained in the reaction of the N-hydroxy compound (181a) with hot acetic anhydride (page 147).

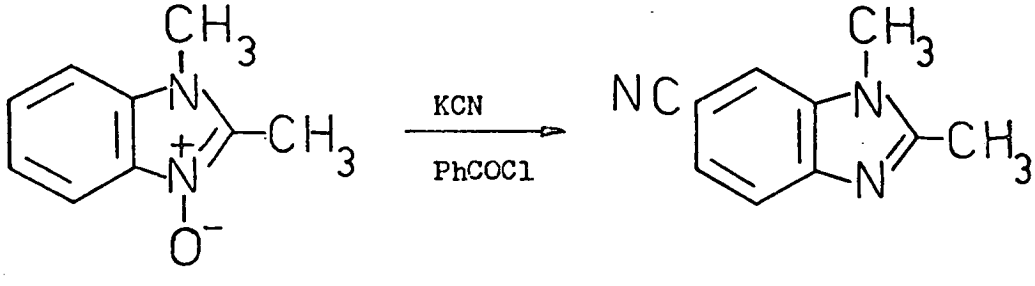
The N-acetoxy compound (190a) also underwent rearrangement to the 5-acetoxy derivative (196a) in good yield when heated in glacial acetic acid. In order to find out whether the N-acetoxy compound (190a) would react with acetate ion, a solution of the compound (190a) in glacial acetic acid was stirred at room temperature with fused sodium acetate. The reaction was worked up to give a moderate yield of the 5-acetoxy derivative (196a). It was noticed that the reaction mixture became dark brown on being heated during the work up and this

suggests that the N-acetoxy compound (190a) did not in fact react with the acetate ion at room temperature but rather was converted into the 5-acetoxy derivative (196a) by heating in the glacial acetic acid during work up.

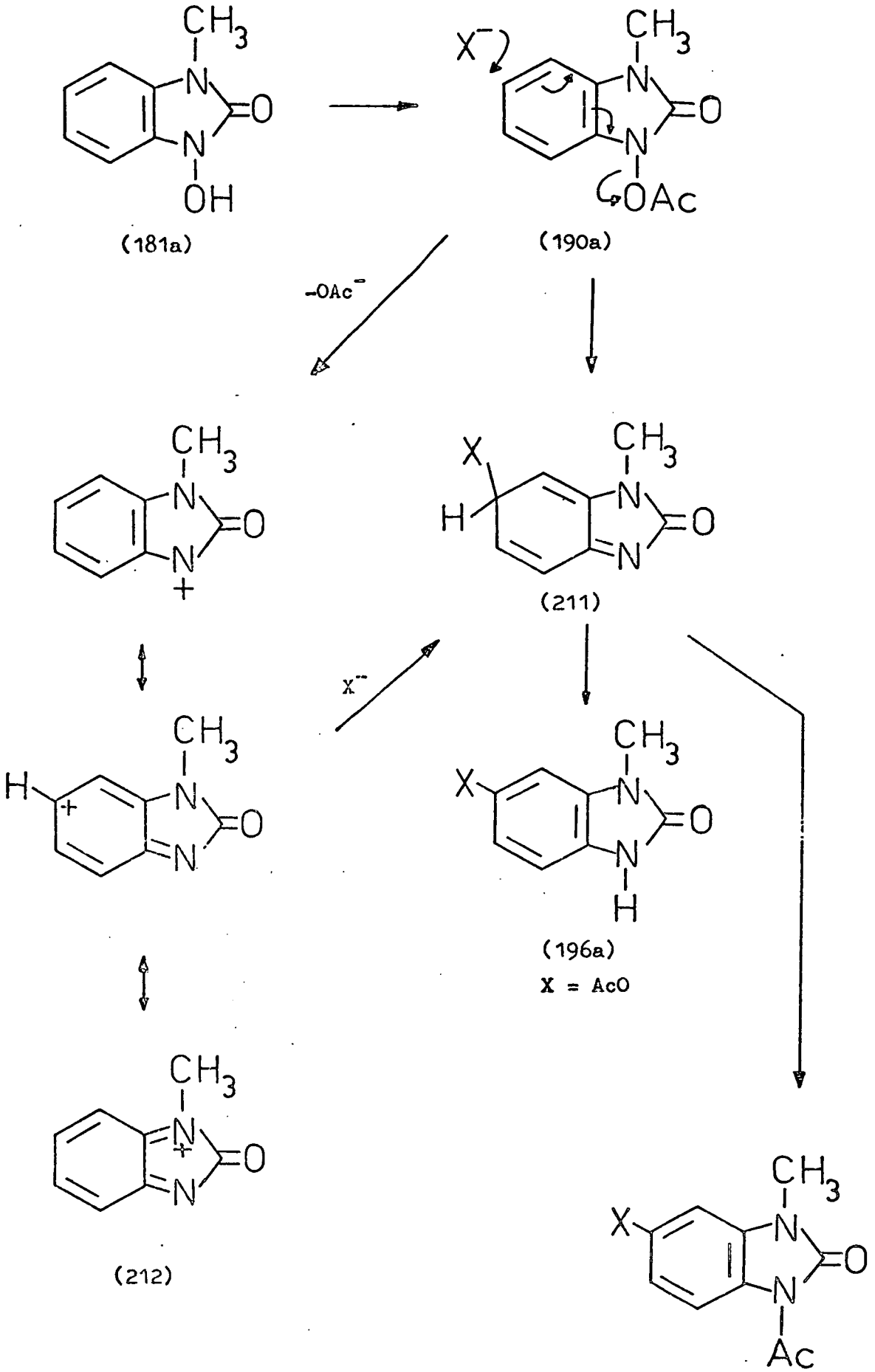
When the N-acetoxy compound (190a) was heated in propionic acid, the product obtained was shown to be a mixture of an acetoxy and a propionyloxy compound by its ^{1}H n.m.r. spectrum. The presence of the propionyloxy compound was clearly shown by the ^{1}H n.m.r. signals at τ 7.25 (quartet) and τ 8.63 (triplet).

The N-acetoxy compound (190a) was recovered unchanged in almost quantitative yield when it was heated for a short time with acetic anhydride. In view of the fact that the compound (190a) has been shown to undergo rearrangement to the 5-acetoxy derivative (196a) when heated in ethanol, toluene and glacial acetic acid, it is probable that in this reaction with acetic anhydride, the reaction time was not long enough and the conditions were not vigorous enough.

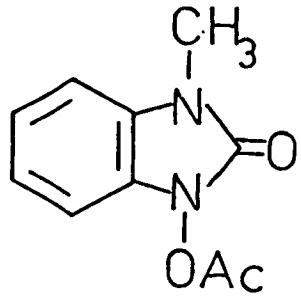
In an attempt to react the N-acetoxy compound (196a) with other nucleophiles, it was treated with ethanolic sodium cyanide. A good yield of the corresponding N-hydroxy compound (181a) was obtained. Thus, hydrolysis of the N-acetoxy group to the N-hydroxy group takes place rather than nucleophilic substitution by cyanide ion. Substitution in the 5-position of an N-oxygenated benzimidazole by cyanide ion is exemplified by the reaction (209→210) reported by Kano.[52]



(209) (210)

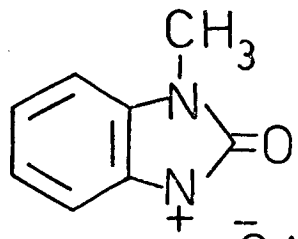

CH3
N
O
N
OH
X⁻
OAc
(181a)
(190a)
-OAc⁻
H
(211)
X⁻
(196a)
X = AcO
(212)
Ac
(196c, X = Cl)
(196h, X = Br)

scheme 49



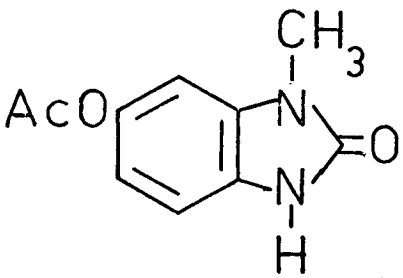
(190a)

ionisation



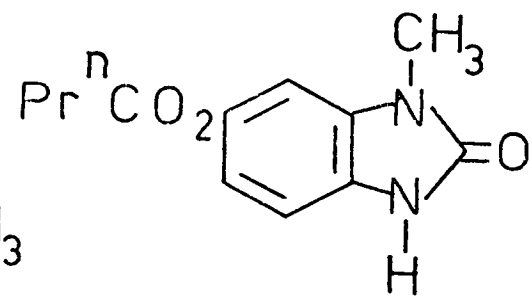
(213)

Pr^nCO_2H

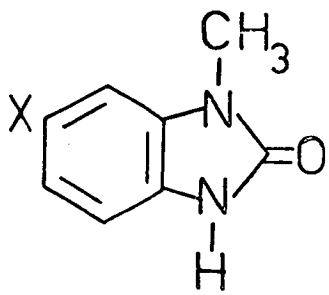


(196a)

X^-



(196r)



(196p, X = Cl)

(196q, X = Br)

scheme 50

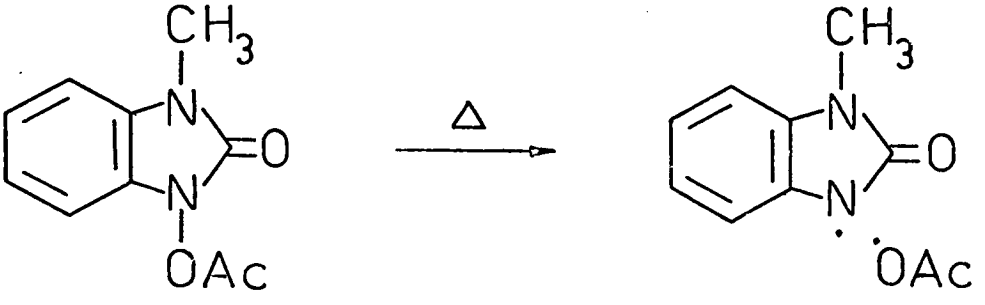
4.6 Discussion of Reaction Mechanisms

The reactions of the N-hydroxybenzimidazolinones (181 a-c) with acetylating agents at elevated temperatures are explicable by the reaction mechanism outlined in scheme 49 for the N-methyl compound (181a). The initial step involves the formation of the N-acetoxy compound (190a) which can undergo nucleophilic attack at the 5-position with simultaneous loss of the acetoxy leaving group to give the intermediate (211). The intermediate (211) gives the observed products (196a, X = AcO), (196c, X = Cl) and (196h, X = Br) as shown. Alternatively, ionisation of the N-acetoxy compound (190a) could occur giving the resonance stabilised nitrenium cation (212).[47] Nucleophilic attack at the 5-position in the latter would yield the intermediate (211) which then gives the observed products as shown in scheme 49. In the acetyl chloride and acetyl bromide reactions, subsequent acetylation at N-1 occurs to give N-acetyl derivatives (196 c and h).

However, the demonstration of the apparently purely thermal rearrangement of the N-acetoxy compounds (190 a and b) to the 5-acetoxy derivatives (196 a and b) puts a different complexion on the results and suggests that all of the reactions go according to the mechanism in scheme 50. As shown in scheme 50, ionisation of the N-acetoxy compound (190a) gives the ion-pair (213). If no other nucleophile is present, then the ion-pair (213) rearranges to the 5-acetoxy derivative (196a). This process could be <u>intramolecular</u> (tight ion-pair) or <u>intermolecular</u> (loose ion-pair). In the acetyl chloride and acetyl bromide reactions, chloride ion and bromide ion may be present and the ion-pair (213) undergoes nucleophilic substitution at the 5-position to give the 5-chloro

and 5-bromo derivatives (196 p and q) respectively. As mentioned previously, these are acetylated to the N-acetyl derivatives (196 c and h) respectively during the course of the reaction. The fact that the N-acetoxy compound (190a) rearranges in propionic acid to give a product containing a propionoyloxy group (196r) suggests that the rearrangement is intermolecular.

A radical pair process for the rearrangement cannot be excluded (190a→214) . However, this is unlikely in view of the subsequent

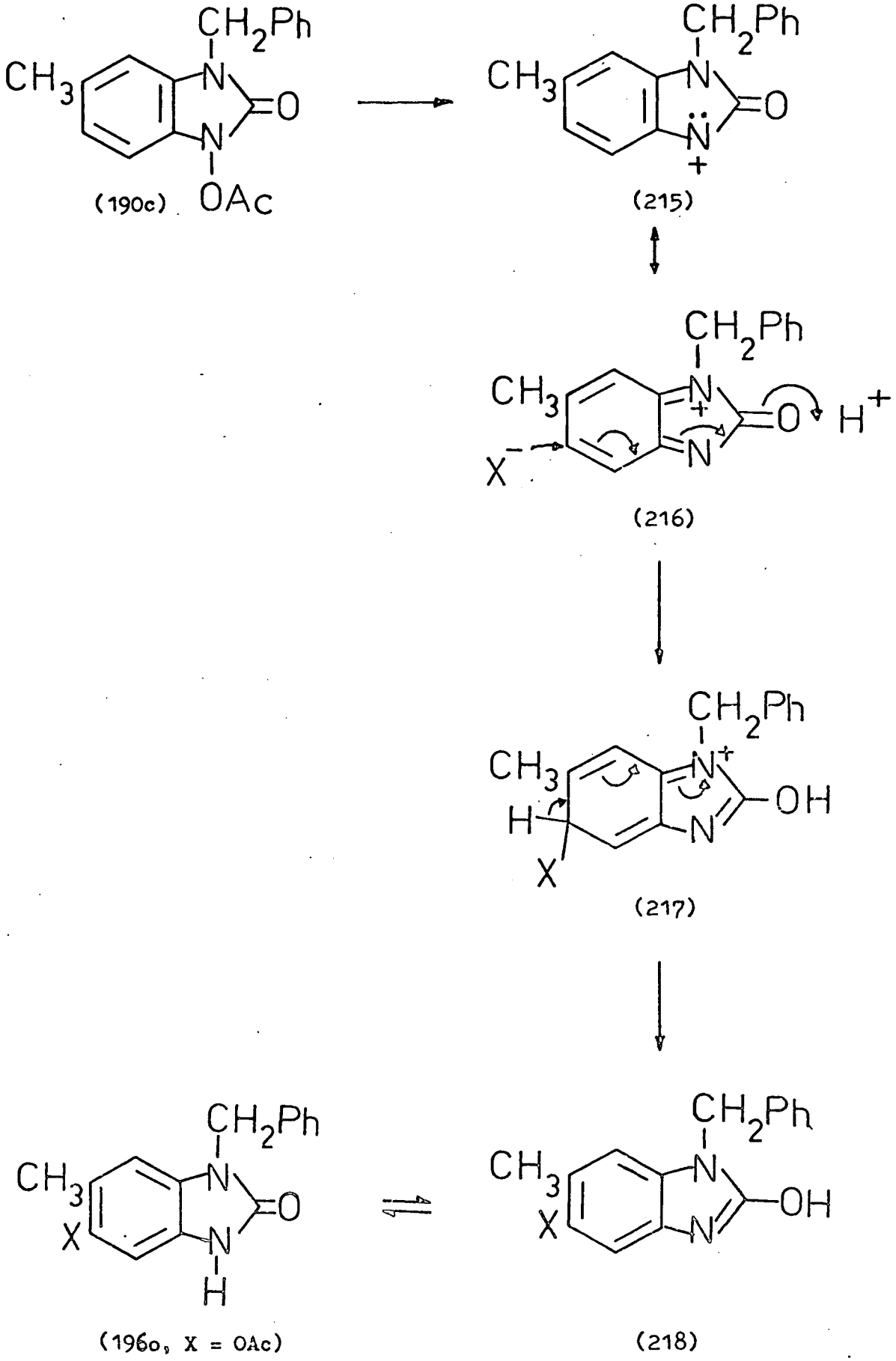


(190a) (214)

attack by what must be chloride ion and bromide ion in the acetyl chloride and acetyl bromide reactions. Under the conditions used in these reactions, the presence of free radicals is somewhat unlikely.

The acetyl chloride and acetyl bromide reactions could be concerted [(181a)→(190a)→(211)→(196 c and h)] (scheme 49) but the thermal rearrangement of the N-acetoxy compound (190a) in toluene and ethanol must be stepwise and probably ionic rather than free radical. The rearrangement in acetic acid could be concerted or stepwise. Further work is required to clarify the situation and will be going ahead in due course.

If the process (190a→196a) is an intermolecular rearrangement, it should be possible to introduce other nucleophiles into the 5-position of the compound (190a) by reacting the compound (190a)

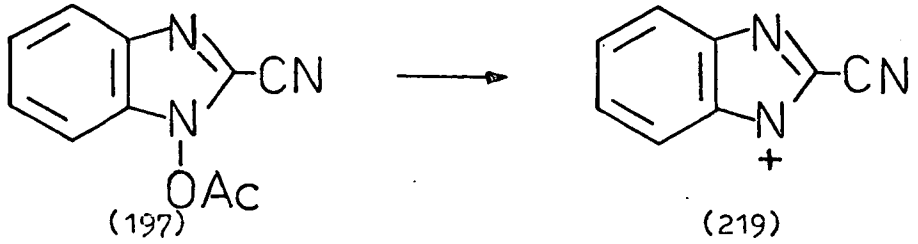


scheme 51

with nucleophiles. However, in the case of cyanide ion at least, the demonstration of such a process was precluded by the preferential hydrolysis of the N-acetoxy group which occurred (page 159). Once hydrolysis of the N-acetoxy group has taken place, nucleophilic substitution will not occur readily since the hydroxyl group is not such a good leaving group as the acetoxyl group.

The reaction of the 5-methyl compound (181d) with acetyl chloride to give the 6-chloro derivative (196f) and the rearrangement of the 5-methyl-N-acetoxy compound (190c) to give the 6-acetoxy derivative (196o) is unusual and is difficult to rationalise on the basis of the mechanisms outlined in schemes 49 and 50. A tentative suggestion for a mechanism which would explain substitution in the 6-position of (190c) is outlined in scheme 51. Ionisation of the N-acetoxy compound (190c) gives the nitrenium cation [(215)↔(216)]. Nucleophilic attack at the 6-position by X^- with the simultaneous gain of a proton at the 2-position gives the intermediate (217). The elimination of a proton from (217) gives (218) which is tautomeric with the observed product (196o).

The 1-hydroxy 2-cyanobenzimidazole (178a) is much less reactive towards acetylating agents than are the N-hydroxybenzimidazolinones (181). This could be due to the fact that ionisation of the N-acetoxy compound (197) would give the nitrenium cation (219) which cannot be



(197) (219)

stabilised by resonance. The nitrenium cation (212) derived from ionisation of the N-acetoxy compound (190a) is resonance stabilised (scheme 49).

Chapter Five

Experimental Section - N-Oxygenated Benzimidazoles

5.1 The Synthesis of N-Benzyl-2-nitroanilines

The 2-nitrochlorobenzene derivative (170) (0.1 mol), benzylamine (10.6 g, 10.7 ml, 0.1 mol) and anhydrous potassium carbonate (7.0 g, 0.05 mol) were stirred at 150° for 2 h. The reaction mixture was cooled, extracted with boiling ethanol (150 ml) and hot filtered. The N-benzyl-2-nitroanilines (167 c-g) crystallised from the ethanol and were collected by filtration, washed with water (20 ml) and dried in vacuo.

(a) N-Benzyl-2-nitroaniline (167c) was prepared from 2-nitrochlorobenzene (170a) as an orange crystalline solid (65%), m.p. 74° (lit.[64] 74°) (from ethanol).

(b) N-Benzyl-4-chloro-2-nitroaniline (167e) was prepared from 2,5-dichloronitrobenzene (170c) as orange needles (64%), m.p. 78° (from ethanol) (lit.[65] 79°), ν_{max} 3450 w (NH), 1520 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 1.64 (1H, broad singlet, NH), 1.86 (1H, d, J_{meta} 2.0 Hz, H-3), 2.60-2.80 (6H, m, ArH), 3.27 (1H, d, J_{ortho} 8.0 Hz, H-6) and 5.51 (2H, d, J_{CH-NH} 6.0 Hz, CH_2), M^+ 262 (264).

(c) N-Benzyl-5-chloro-2-nitroaniline (167f) was prepared from 2,4-dichloronitrobenzene (170d) as described above as an orange crystalline solid (54%), m.p. 102° (from ethanol) (lit.[65] 102°), ν_{max} 3400 w (NH), 1505 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 1.54 (1H, broad singlet, NH), 1.87 (1H, d, J_{ortho} 8.0 Hz, H-3), 2.64 (5H, s, ArH), 3.16 (1H, d, J_{meta} 2.0 Hz, H-6), 3.37 (1H, dd, J_{ortho} 8.0 Hz, J_{meta} 2.0 Hz, H-4) and 5.50 (2H, d, J_{CH-NH} 6.0 Hz, CH_2).

(d) N-Benzyl-5-methyl-2-nitroaniline (167d) was prepared from 2-chloro-4-methylnitrobenzene (170b) as described above as orange plates (65%), m.p. 102° (from ethanol), ν_{max} 3430 w (NH), 1505 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 1.58 (1H, broad singlet, NH), 1.94 (1H,

d, J_{ortho} 8.5 Hz, H-3), 2.60-2.90 (5H, m, ArH), 3.41 (1H, singlet, H-6), 3.54 (1H, dd, J_{ortho} 8.5 Hz, J_{meta} 2.0 Hz, H-4), 5.50 (2H, d, J_{CH-NH} 6.0 Hz, CH_2) and 7.74 (3H, s, CH_3).

Found: C, 69.5; H, 5.8; N, 11.2%

$C_{14}H_{14}N_2O_2$ requires: C, 69.4; H, 5.8; N, 11.6%.

(e) N-Benzyl-6-chloro-2-nitroaniline (167e)

2,3-Dichloronitrobenzene (170e) (38.4 g, 0.2 mol), anhydrous potassium carbonate (14 g, 0.1 mol) and benzylamine (31.8 g, 32.1 ml, 0.3 mol) were stirred at 150° for 2 h. The mixture was cooled, extracted with hot ethanol (200 ml) and hot filtered. No solid crystallised from the ethanol extract on cooling and the solvent was evaporated giving a red oil which was extracted into chloroform. The extract was washed with 5M aqueous hydrochloric acid (20 ml) and evaporated to give a red gum (56 g) which was shown to be contaminated with benzaldehyde [t.l.c. (light petroleum-benzene) and i.r. comparison with an authentic sample]. The red gum was redissolved in chloroform and the extract was stirred for 12 h with saturated aqueous sodium bisulphite solution (50 ml). Evaporation of the extract gave N-benzyl-6-chloro-2-nitroaniline (167e) as a red oil (48.3 g) (92%), ν_{max} (liquid film) 3330 (NH), 1530 and 1340 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.13 (1H, dd, J_{ortho} 8.5 Hz, J_{meta} 2.0 Hz, H-3), 2.52 (1H, dd, J_{ortho} 8.0 Hz, J_{meta} 2.0 Hz, H-5), 2.64-2.80 (5H, m, ArH), 3.23 (1H, d, J_{ortho} 8.0 Hz, H-4) and 5.46 (2H, d, J_{CH-NH} 6.0 Hz, CH_2).

The Synthesis of 5-Chloro-1-hydroxy-2-phenylbenzimidazole (187)

N-Benzyl-5-chloro-2-nitroaniline (167f) (0.4 g, 0.0015 mol) and sodium hydroxide (0.3 g) were heated in methanol (12 ml) on a boiling water bath for 5 h. The reaction mixture was cooled, concentrated to half the original volume and neutralised with 5M aqueous

hydrochloric acid. The cream precipitate was collected and boiled for 5 min with water and recollected to give the benzimidazole (187) (0.29 g) (78%), m.p. 225° (lit.[69] 206°), ν_{max} 3350 br (OH).

5.2 The Synthesis of 2-Nitroanilinoacetonitriles

(a) 2-Nitroanilinoacetonitrile (165a)

2-Nitroaniline (164a) (7.0 g, 0.05 mol), paraformaldehyde (4.5 g, 0.15 g), sodium cyanide (7.35 g, 0.15 mol) and powdered anhydrous zinc chloride sticks (52.5 g, 0.375 mol) were stirred in glacial acetic acid (125 ml) at 50° for 1.0 h. The reaction mixture was diluted with warm water (175 ml) and stirred in an ice bath for 0.5 h. The yellow solid which crystallised from the reaction mixture was collected, washed with water (50 ml) and dried in vacuo to yield 2-nitroanilinoacetonitrile (165a) (7.43 g) (84%), m.p. 140° (lit.[62] 140.5°), ν_{max} 3450 (NH), 1520 and 1360 (NO_2) cm^{-1}.

(b) 4-Chloro-2-nitroanilinoacetonitrile (165b)

4-Chloro-2-nitroaniline (164b) (8.6 g, 0.05 mol) was stirred with paraformaldehyde (4.5 g, 0.15 mol), sodium cyanide (7.35 g, 0.15 mol) and anhydrous zinc chloride (52.5 g, 0.375 mol) in glacial acetic acid (125 ml) for 0.5 h.

The reaction mixture was worked up as described in experiment 5.2(a) to give 4-chloro-2-nitroanilinoacetonitrile (165b) as yellow prisms (9.8 g) (94%), m.p. 154° (from ethanol) ν_{max} 3330 (NH), 2220 w (CN), 1520 and 1340 (NO_2) cm^{-1}, τ ($CF_3.CO_2H$) 1.70 (1H, d, J_{meta} 2.5 Hz, H-3), 2.32 (1H, dd, J_{ortho} 9.0 Hz, J_{meta} 2.5 Hz, H-5), 2.96 (1H, d, J_{ortho} 9.0 Hz, H-6) and 5.46 (2H, s, CH_2).

Found: C, 45.2; H, 2.8; N, 19.9%

$C_8H_6ClN_3O_2$ requires: C, 45.4; H, 2.8; N, 19.9%

(c) 4-Methyl-2-nitroanilinoacetonitrile (165c)

4-methyl-2-nitroaniline (164c) (7.60 g, 0.05 mol) was stirred with paraformaldehyde (4.5 g, 0.15 mol), sodium cyanide (7.35 g, 0.15 mol) and anhydrous zinc chloride (52.5 g, 0.375 mol) in glacial acetic acid (125 ml) for 6 h.

The reaction mixture was worked up as described in experiment 5.2(a) to give a yellow solid (8.3 g), m.p. 108°-130° (from ethanol) ν_{max} 3400 (NH), 2260 w (CN), 1530 and 1340 (NO_2) cm^{-1} the t.l.c. (chloroform; ether; benzene) of which showed a single component but whose ^1H n.m.r. spectra showed it to be a 2:1 mixture of N,N-bis(cyanomethyl)-4-methyl-2-nitroaniline (166a) and 4-methyl-2-nitroanilinoacetonitrile (165c) respectively.

τ($CF_3.CO_2H$) 1.76-1.90 (m, ArH), 2.10-2.28 (m, ArH), 2.90-3.02 (m, ArH), 5.44 (1 unit, s, CH_2), 5.58 (4 units, s, CH_2) 7.49 (3 units, s, CH_3) and 7.60 (1.5 units, s, CH_3).

τ[$(CD_3)_2SO$] 1.80-3.00 (m, ArH), 5.46 (1 unit, d, J 7.0 Hz, CH_2), 5.65 (4 units, s, CH_2), 7.60 (s, CH_3) and 7.72 (s, CH_3).

The mass spectrum contained peaks at 230 and 191 attributable to N,N-bis(cyanomethyl)-4-methyl-2-nitroaniline (166a) and 4-methyl-2-nitroanilinoacetonitrile (165c) respectively. The mixture crystallised unchanged from ethanol.

(d) 4-Methoxy-2-nitroanilinoacetonitrile (165d)

4-methoxy-2-nitroaniline (164d) (8.4 g, 0.05 mol) was stirred with paraformaldehyde (4.5 g, 0.15 mol), sodium cyanide (7.35 g, 0.15 mol) and anhydrous zinc chloride (52.5 g, 0.375 mol) in glacial acetic acid (125 ml) for 1 h.

The reaction mixture was worked up as described in experiment 5.2(a) to give an orange solid (8.2 g), m.p. 45-55°, ν_{max} 3350 (NH),

2200 w (CN), 1520 and 1360 (NO_2) cm^{-1}, the t.l.c. (chloroform; ether; benzene) of which showed a single component.

The orange solid (8.0 g) was crystallised from methanol to give 4-methoxy-2-nitroanilinoacetonitrile (165d) as orange prisms (0.77 g) (7%), m.p. 148° (from ethanol-glacial acetic acid), ν_{max} 3350 (NH) 2220 w (CN), 1520 and 1360 (NO_2) cm^{-1}, τ [$(CD_3)_2SO$] 1.94 (1H, broad triplet, J_{NH-CH} 7.0 Hz, NH), 2.40 (1H, d, J_{meta} 3.0 Hz, H-3), 2.60 (1H, dd, J_{meta} 3.0 Hz, J_{ortho} 9.0 Hz, H-5), 2.86 (1H, d, J_{ortho} 9.0 Hz, H-6), 5.46 (2H, d, J_{CH-NH} 7.0 Hz, CH_2) and 6.24 (3H, s, $O.CH_3$).

Found: C, 52.1; H, 4.4; N, 20.4%: M^+ 207

$C_9H_9N_3O_3$ requires: C, 52.2; H, 4.4; N, 20.3%: M 207.

The methanol mother liquors were evaporated and the orange solid (7.2 g) was crystallised several times from methanol to give a pure sample of N,N-bis(cyanomethyl)-4-methoxy-2-nitroaniline (166b) as yellow prisms (0.1 g), m.p. 63° (from light petroleum-benzene) ν_{max} 2220 w (CN), 1540 and 1350 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.44 (1H, d, J_{ortho} 9.0 Hz, H-6), 2.70-2.94 (2H, m, ArH), 5.91 (4H, s, CH_2) and 6.16 (3H, s, $O.CH_3$).

Found: C, 53.7; H, 4.1; N, 22.9%: M^+ 246

$C_{11}H_{10}N_4O_3$ requires: C, 53.7; H, 4.1; N, 22.8%: M 246.

(e) α-(2-Nitroanilino)propionitrile (165e)

2-Nitroaniline (7.0 g, 0.05 mol) was stirred with acetaldehyde (6.6 g, 8.3 ml, 0.15 mol), sodium cyanide (7.35 g, 0.15 mol) and anhydrous zinc chloride (52.5 g, 0.375 mol) in acetic acid (125 ml) for 6 h.

The reaction mixture was worked up as described in experiment 5.2(a). The yellow solid was collected and combined with a second crop which separated from the filtrate on standing to give

α-(2-nitroanilino)propionitrile (165e) as yellow plates (7.8 g) (80%), m.p. 84° (from ethanol), ν_{max} 3370 (NH), 2280 w (CN), 1530 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 1.78 (1H, q, J_{ortho} 9.0 Hz, J_{meta} 2.0 Hz, ArH), 2.0-2.24 (1H, broad, NH), 2.30-2.52 (1H, m, ArH), 2.96-3.24 (2H, m, ArH), 5.54 (1H, quintet, J 8.0 Hz, CH) and 8.18 (3H, d, J 7.0 Hz, CH_3).

Found: C, 56.4; H, 4.8; N, 22.0%

$C_9H_9N_3O_2$ requires: C, 56.5; H, 4.7; N, 22.0%

(f) α-(2-Nitroanilino)phenylacetonitrile (165f)

2-Nitroaniline (7.0 g, 0.05 mol) was stirred with redistilled benzaldehyde (15.3 ml, 0.15 mol), sodium cyanide (7.35 g, 0.15 mol) and anhydrous zinc chloride (52.5 g, 0.375 mol) in glacial acetic acid (125 ml) for 6 h.

The reaction mixture was worked up as described in experiment 5.2(a) to give α-(2-nitroanilino)phenylacetonitrile (165f) as yellow prisms (12.0 g) (94%), m.p. 126° (from ethanol), ν_{max} 3400 (NH), 1520 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 1.66-1.86 (2H, m, ArH and NH), 2.28-3.26 (8H, m, ArH) and 4.41 (1H, d, J_{CH-NH} 7.0 Hz, CH).

Found: C, 66.8; H, 4.4; N, 16.8%

$C_{14}H_{11}N_3O_2$ requires: C, 66.4; H, 4.4; N, 16.6%.

5.3 The Synthesis of N-Substituted—2-nitroanilinoacetonitriles

(a) N-Methyl-2-nitroanilinoacetonitrile (168a)

(i) N-Methyl-2-nitroaniline (167a) (1.52 g, 0.01 mol), paraformaldehyde (0.9 g, 0.03 mol), sodium cyanide (1.47 g, 0.03 mol) and anhydrous zinc chloride sticks (10.5 g, 0.075 mol) were stirred in glacial acetic acid (25 ml) at 50° for 6 h. Dilution with water (35 ml) and extraction with chloroform gave an orange gum (1.67 g) which was

shown by t.l.c. (benzene) to contain two components and was chromatographed on alumina.

Elution with light petroleum gave N-methyl-2-nitroaniling (167a) (0.03 g) (2%), m.p. 36° (lit. 37°), identical (i.r. spectrum) with an authentic sample. Elution with light petroleum-toluene (2:1) gave N-methyl-2-nitroanilinoacetonitrile (168a) as a pale yellow oil (1.04 g) (54%), ν_{max} (liquid film) 2325 w (CN), 1540 and 1370 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.12-2.85 (4H, m, ArH), 5.92 (2H, s, CH_2) and 7.07 (3H, s, N.CH_3), M^+ 191 (M 191).

(ii) Reaction (i) was repeated using a reaction time of 1 h. Work up of the mixture as described above gave N-methyl-2-nitroanilino-acetonitrile (168a) as a yellow gum (99%) which was identical (i.r. spectrum) with the sample obtained in (i) above and did not require purification by chromatography.

(b) N-Phenyl-2-nitroanilinoacetonitrile (168b)

2-Nitrodiphenylamine (167b) reacted with paraformaldehyde, sodium cyanide and anhydrous zinc chloride in glacial acetic acid as described in experiment 5.3(a)(i) above to give a red gum (2.84 g) which was shown by t.l.c. (benzene) to be a three component mixture and was chromatographed on alumina.

Elution with light petroleum-toluene gave phenazine (169) (0.01 g), m.p. and mixed m.p. 176° (from ethanol) (lit. 177°) identical (i.r. spectrum) with an authentic sample. Further elution with light petroleum-toluene (3:1) gave N-phenyl-2-nitroanilino-acetonitrile (168b) as a red oil (1.36 g) (54%), ν_{max} (liquid film) 1540 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.00-3.40 (9H, m, ArH), 5.45 (2H, s, CH_2), M^+ 253 (M 253).

Elution with toluene gave an unidentified orange solid (1.0 g)

(38%), m.p. 147° (orange plates from ethanol-glacial acetic acid), ν_{max} 1530 and 1350 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.02-3.44 (21 units, m, ArH), 5.46 (4 units, s, CH_2) and 6.18 (2 units, s, CH_2).

Found: C, 67.2; H, 4.3; N, 16.8%: M^+ 518

$C_{29}H_{22}N_6O_4$ requires: C, 67.2; H, 4.3; N, 16.2%: M 518.

(c) N-Benzyl-2-nitroanilinoacetonitrile (168c)

N-Benzyl-2-nitroaniline (167c) reacted with paraformaldehyde, sodium cyanide and anhydrous zinc chloride in glacial acetic acid as described in experiment 5.3(a)(i) above to give a yellow oil (2.85 g) which was chromatographed on alumina. Elution with light petroleum gave benzyl acetate (0.21 g) identical (i.r. and ^1H n.m.r. spectra) with an authentic sample. Further elution with light petroleum gave N-benzyl-2-nitroaniline (167c) (0.02 g) (1%), m.p. 74° (lit.[64] 74°) identical (i.r. spectrum) with an authentic sample.

Elution with light petroleum-toluene (4:1) gave N-benzyl-2-nitroanilinoacetonitrile (168c) as yellow plates (1.75 g) (66%), m.p. 60° (from light petroleum-benzene), ν_{max} 2300 w (CN), 1540 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.16-2.80 (9H, m, ArH), 5.70 (2H, s, CH_2) and 6.08 (2H, s, CH_2).

Found: C, 67.5; H, 4.9; N, 15.5%: M^+ 267

$C_{15}H_{13}N_3O_2$ requires: C, 67.4; H, 4.9; N, 15.7%: M 267

Elution with toluene gave 2-nitroanilinoacetonitrile (165a) (0.43 g) (24%), m.p. 140° (lit.[62] 140.5°) identical (i.r. spectrum) with an authentic sample.

(d) N-Benzyl-5-methyl-2-nitroanilinoacetonitrile (168d)

N-Benzyl-5-methyl-2-nitroaniline (167d), paraformaldehyde, sodium cyanide and anhydrous zinc chloride were stirred in glacial

acetic acid as described in experiment 5.3(a)(i) above. After 20 min, the t.l.c. (benzene) of the reaction mixture indicated complete consumption of the starting amine. The reaction mixture was diluted with water (35 ml) and extracted with chloroform to give a yellow gum (2.8 g) which was shown by t.l.c. (benzene) to be a two component mixture and was chromatographed on alumina.

Elution with light petroleum-toluene (3:1) gave N-benzyl-5-methyl-2-nitroanilinoacetonitrile (168d) as a yellow oil (2.6 g) (92%), ν_{max} (liquid film) 2230 w (CN), 1530 and 1350 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.29 (1H, d, J 7.0 Hz, ArH), 2.50-3.00 (7H, m, ArH), 5.70 (2H, s, CH_2), 6.07 (2H, s, CH_2) and 7.57 (3H, s, CH_3).

Elution with toluene gave 5-methyl-2-nitroanilinoacetonitrile (165g) as yellow plates (0.13 g) (7%), m.p. 163° (from ethanol-glacial acetic acid), ν_{max} 3360 w (NH), 1500 and 1340 (NO_2) cm^{-1}, τ ($CF_3.CO_2H$) 1.80 (1H, d, J_{ortho} 8.5 H_5, H-3), 3.08-3.26 (2H, m, ArH), 5.46 (2H, s, CH_2) and 7.51 (3H, s, CH_3).

Found: C, 56.5; H, 4.7; N, 21.7%

$C_9H_9N_3O_2$ requires: C, 56.5; H, 4.7; N, 22.0%.

(e) N-Benzyl-4-chloro-2-nitroanilinoacetonitrile (168e)

N-Benzyl-4-chloro-2-nitroaniline (167e) reacted with paraformaldehyde, sodium cyanide and anhydrous zinc chloride in glacial acetic acid as described in experiment 5.3(a)(i). After 30 min, the t.l.c. (benzene) of the reaction mixture indicated that the starting material had all been consumed and the reaction mixture was worked up to give a yellow gum (2.5 g) which was chromatographed on alumina.

Elution with light petroleum-toluene (4:1) gave benzyl acetate (0.01 g) identical (i.r. spectrum) with an authentic sample.

Elution with light petroleum-toluene (2:1) gave N-benzyl-4-chloro-2-nitroanilinoacetonitrile (168e) as a yellow oil (2.53 g) (84%), ν_{max} (liquid film) 2300 w (CN), 1540 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.24-2.80 (8H, m, ArH), 5.72 (2H, s, CH_2) and 6.08 (2H, s, CH_2).

Elution with toluene-ether (1:1) gave an intractable brown gum (0.3 g).

(f) N-Benzyl-5-chloro-2-nitroanilinoacetonitrile (168f)

N-Benzyl-5-chloro-2-nitroaniline (167f) reacted with paraformaldehyde, sodium cyanide and anhydrous zinc chloride in glacial acetic acid as described in experiment 5.3(a)(i) above. The yellow gummy solid (3.43 g) which was obtained was shown by t.l.c. (chloroform) to be a two component mixture and was chromatographed on alumina.

Elution with light petroleum-toluene (4:1) gave an orange liquid (0.37 g), ν_{max} 3400 w (NH), 1740 (CO), 1505 and 1360 (NO_2) cm^{-1}, which was shown by t.l.c. (benzene and chloroform) to be a mixture of benzyl acetate and the starting amine (167f).

Elution with light petroleum-toluene (2:1) gave N-benzyl-5-chloro-2-nitroanilinoacetonitrile (168f) as yellow elongated prisms (1.38 g) (44%), m.p. 78° (from light petroleum-benzene), ν_{max} 1530 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.23 (1H, d, J_{ortho} 8.5 Hz, H-3), 2.47 (1H, d, J_{meta} 2.0 Hz, H-6), 2.60-2.80 (6H, m, ArH), 5.69 (2H, s, CH_2) and 6.06 (2H, s, CH_2).

Found: C, 59.3; H, 3.9; N, 14.0%

$C_{15}H_{12}ClN_3O_2$ requires: C, 59.7; H, 4.0; N, 13.9%.

Elution with toluene gave 5-chloro-2-nitroanilinoacetonitrile (165h) as yellow prisms (0.29 g) (14%), m.p. 182° (from ethanol-glacial acetic acid), ν_{max} 3400 w (NH), 1505 and 1360 (NO_2) cm^{-1},

τ ($CF_3.CO_2H$) 1.73 (1H, d, J_{ortho} 9.0 Hz, H-5), 2.92 (1H, d, J_{meta} 2.0 Hz, H-8), 3.05 (1H, dd, J_{ortho} 9.0 Hz, J_{meta} 2.0 Hz, H-4) and 5.46 (2H, s, CH_2).

Found: C, 45.1; H, 2.8; N, 19.9%

$C_8H_6ClN_3O_2$ requires: C, 45.4; H, 2.8; N, 19.9%.

Elution with methanol gave 5-chloro-2-nitroanilinoacetamide (171) as yellow prisms (0.1 g) (4%), m.p. 215° (from ethanol-glacial acetic acid), ν_{max} 3425 and 3175 (NH), 1680 (CO), 1505 and 1370 (NO_2) cm^{-1}, τ($CF_3.CO_2H$) 1.76 (1H, d, J_{ortho} 9.0 Hz, H-3), 2.0-2.40 (2H, broad singlet, NH_2), 3.04-3.20 (2H, m, ArH) and 5.61 (2H, s, CH_2)

Found: C, 42.5; H, 3.5; N, 18.0%: M^+ 229 (231)

$C_8H_8ClN_3O_3$ requires: C, 41.8; H, 3.5; N, 18.3%: M 229.5

(g) N-Benzyl-6-chloro-2-nitroanilinoacetonitrile (168g)

N-Benzyl-6-chloro-2-nitroaniline reacted with paraformaldehyde, sodium cyanide and anhydrous zinc chloride in glacial acetic acid as described in experiment 5.3(a)(i). After 30 min, the t.l.c. (benzene) of the reaction mixture indicated complete consumption of the starting amine. The reaction mixture was worked up to give an orange gum (3.0 g) which was chromatographed on alumina.

Elution with light petroleum-toluene (2:1) gave N-benzyl-6-chloro-2-nitroanilinoacetonitrile (168g) as a yellow oil (2.87 g) (95%), ν_{max} (liquid film) 2220 w (CN), 1530 and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.30-2.86 (8H, m, ArH), 5.66 (2H, s, CH_2) and 5.98 (2H, s, CH_2).

Elution with methanol gave an unidentified intractable brown gum (0.09 g).

The Attempted Synthesis of Phenazine

2-Nitrodiphenylamine (167b) (2.14 g, 0.01 mol) and anhydrous zinc chloride sticks (10.5 g, 0.075 mol) were stirred in glacial acetic acid (25 ml) at 50° for 6 h. The reaction mixture was diluted with water (35 ml) and the orange solid was collected and washed with water to yield the starting amine (167b) (2.05 g) (96%), identical (i.r. spectrum) with an authentic sample.

5.4 The Attempted Synthesis of α,N-Disubstituted-2-nitroanilino-acetonitriles

(a) α-(N-Benzyl-2-nitroaniline)phenylacetonitrile (172c)

(i) N-Benzyl-2-nitroaniline (167c) (2.28 g, 0.01 mol), sodium cyanide (1.5 g, 0.03 mol), redistilled benzaldehyde (3.0 ml, 0.03 mol) and anhydrous zinc chloride (10.5 g, 0.075 mol) were stirred in glacial acetic acid (25 ml) at 50° for 6 h. The mixture was diluted with water (35 ml) and stirred in an ice bath for 0.5 h. The orange crystalline solid was collected to afford the starting amine (167c) (1.94 g) (85%), m.p. 74° (lit.[64] 74°), identical (i.r. spectrum) with an authentic sample.

(ii) The experiment (i) was repeated using the same quantities but with stirring at 100° for 6 h. The reaction mixture was diluted with water (35 ml) and extracted with chloroform to give a brown gum (5.3 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture and was chromatographed on alumina.

Elution with light petroleum gave an unidentified brown gum (0.26 g) which smelled of benzaldehyde. Further elution with light petroleum gave a mixture (t.l.c. in benzene) of benzyl acetate and N-benzyl-2-nitroaniline (167c) (0.3 g). Further elution with light

petroleum gave N-benzyl-2-nitroaniline (167c) (0.4 g) (18%), m.p. 74° (lit.[64] 74°), identical (i.r. spectrum) with an authentic sample.

Elution with increasingly more polar solvents gave small amounts of unidentified brown gums (total 1.31 g).

(b) α-(N-Methyl-2-nitroanilino)phenylacetonitrile (172a)

N-Methyl-2-nitroaniline (167a) (1.64 g, 0.01 mol), sodium cyanide (1.5 g, 0.03 g), anhydrous zinc chloride (10.5 g, 0.075 mol) and redistilled benzaldehyde (3.0 ml, 0.03 mol) were stirred in glacial acetic acid (25 ml) at 50° for 6 h. The reaction mixture was diluted with water (35 ml) to yield an orange crystalline solid which was collected and washed with water to yield N-methyl-2-nitroaniline (167a) (0.7 g) (43%), m.p. 36° (lit. 37°), identical (i.r. spectrum) with an authentic sample.

The mother liquors were neutralised by the addition of solid sodium hydrogen carbonate and extracted with chloroform to give a red gum (4.2 g) which on trituration with light petroleum gave a further crop of the N-methyl-2-nitroaniline (167a) (0.80 g) (49%), identical (i.r. spectrum) with the first crop.

(c) α-(N-Phenyl-2-nitroanilino)propionitrile (172b)

2-Nitrodiphenylamine (167b) (5.35 g, 0.025 mol), sodium cyanide (3.7 g, 0.075 mol), anhydrous zinc chloride (26.3 g, 0.19 mol) and acetaldehyde (4.2 ml, 0.075 mol) were stirred in glacial acetic acid (60 ml) at 50° for 6 h. The mixture was diluted with water (80 ml) and extracted with chloroform. The extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to give a red gum (6.1 g) which was shown by t.l.c. (chloroform; benzene; ether) to be a mixture of the starting material and acetaldehyde.

5.5 The Synthesis of 2-Cyano-1-hydroxybenzimidazoles

(i) 2-Cyano-1-hydroxybenzimidazole (178a)

2-Nitroanilinoacetonitrile (165a) (7.85 g, 0.05 mol) was heated under reflux in methanol (50 ml) and a solution of sodium carbonate (2.65 g, 0.025 mol) in water (30 ml) was added dropwise with stirring over 15 min. The reaction mixture was heated under reflux with stirring for 1.5 h, cooled in an ice bath and acidified with concentrated hydrochloric acid. The yellow precipitate was collected, washed with water and dried to yield 2-cyano-1-hydroxybenzimidazole (178a) (6.2 g) (78%), m.p. 234°, ν_{max} 2700-2200 br (OH) and 2260 w (CN) cm^{-1}.

The conditions described in this experiment were used in the following experiments 5.5(ii)-(iv).

The N-hydroxybenzimidazole (178a) (0.5 g, 0.003 mol) was reduced with sodium dithionite (2 x 0.5 g) in 70% v/v aqueous ethanol (100 ml) to 2-cyanobenzimidazole (0.3 g) (70%), m.p. 285° (from glacial acetic acid) (lit.[67] 286°), ν_{max} 3100-2600 br (NH) and 2230 w (CN) cm^{-1}, M^+ 143.

(ii) 6-Chloro-2-cyano-1-hydroxybenzimidazole (178b)

4-Chloro-2-nitroanilinoacetonitrile (165b) (2.11 g, 0.01 mol) gave 6-chloro-2-cyano-1-hydroxybenzimidazole (178b) as cream coloured prisms (1.40 g) (73%), m.p. 242° (from glacial acetic acid), ν_{max} 2700-2300 br (OH) and 2300 w (CN) cm^{-1}, τ ($CF_3.CO_2H$) 1.98 (1H, s, ArH) and 2.15 (2H, m, ArH).

Found: C, 49.6; H, 2.1; N, 21.5%

$C_8H_4ClN_3O$ requires: C, 49.6; H, 2.1; N, 21.7%.

(iii) 2-Cyano-1-hydroxy-6-methoxybenzimidazole (178c)

4-Methoxy-2-nitroanilinoacetonitrile (165d) (0.41 g, 0.002 mol) gave 2-cyano-1-hydroxy-6-methoxybenzimidazole (178c) as cream coloured prisms (0.35 g) (93%), m.p. 265° (from glacial acetic acid), ν_{max} 2700-2300 br (OH) and 2220 w (CN) cm^{-1}, τ ($CF_3.CO_2H$) 2.21 (1H, d, J_{ortho} 9.0 Hz, H-4), 2.46 (1H, dd, J_{ortho} 9.0 Hz, J_{meta} 2.5 Hz, H-5), 2.66 (1H, d, J_{meta} 2.5 Hz, H-7).

Found: C, 57.2; H, 3.5; N, 22.6%: M^+ 189

$C_9H_7N_3O_2$ requires: C, 57.1; H, 3.7; N, 22.2%: M 189.

(iv) 2-Cyano-1-hydroxy-5-methylbenzimidazole (178d)

5-Methyl-2-nitroanilinoacetonitrile (165g) (1.91 g, 0.001 mol) gave 2-cyano-1-hydroxy-5-methylbenzimidazole (178d) as cream prisms (1.7 g) (98%), m.p. 245° (from glacial acetic acid), ν_{max} 3400-2400 br (OH) and 2230 w (CN) cm^{-1}, τ ($CF_3.CO_2H$) 2.04-2.38 (3H, m, ArH) and 7.37 (3H, s, CH_3).

Found: C, 62.4; H, 4.2; N, 24.0%

$C_9H_7N_3O$ requires: C, 62.4; H, 4.1; N, 24.3%.

The Cyclisation of α-(2-Nitroanilino)phenylacetonitrile (165f)

α-(2-Nitroanilino)phenylacetonitrile (165f) (2.53 g, 0.01 mol) was heated under reflux in aqueous methanolic sodium carbonate solution as described in experiment 5.5(i). The reaction mixture was cooled, diluted with water (10 ml) and extracted with chloroform to give a brown gum (1.8 g) which was chromatographed on alumina.

Elution with light petroleum-toluene (3:1) gave an unidentified yellow solid (0.44 g) (17%), m.p. 84° (from light petroleum), ν_{max} 1680-1660, 1530 (NO_2), and 1360 (NO_2) cm^{-1}, τ ($CDCl_3$) 2.02 (1H, dd, J_{ortho} 8.0 Hz, J_{meta} 2.0 Hz, ArH), 2.50-3.10 (7H, m, ArH), 3.33 (1H, dd, J_{ortho} 8.0 Hz, J_{meta} 2.0 Hz, ArH) and 6.01 (3H, s, $C.CH_3$ or $N.CH_3$).

Found: C, 66.2; H, 4.7; N, 11.1%: M^+ 256

$C_{14}H_{12}N_2O_3$ requires: C, 65.6; H, 4.7; N, 10.9%: M 256.

Further elution with light petroleum-toluene (3:1) gave 2-nitroaniline (0.17 g) (12%), m.p. 70° (lit. 72°) identical (i.r. spectrum) with an authentic sample.

Elution with ether gave an unidentified gummy solid (0.21 g) and elution with chloroform gave an intractable brown gum (0.4 g).

The aqueous mother liquors were acidified with concentrated hydrochloric acid and the cream precipitate was collected, washed with water and dried to give 1-hydroxy-2-phenylbenzimidazole (136) (0.43 g) (20%), m.p. 215° (lit.[53] 220°), identical (i.r. spectrum) with an authentic sample.

The Attempted Cyclisation of α-(2-Nitroanilino)propionitrile (165e)

α-(2-Nitroanilino)propionitrile (165e) (3.82 g, 0.02 mol) was heated under reflux in aqueous methanolic sodium carbonate solution as described in experiment 5.5(i) to give a brown gum (2.81 g) which was chromatographed on alumina.

Elution with light petroleum, toluene, ether, chloroform and methanol gave brown intractable gums (total 1.6 g), none of which could be identified.

Acidification of the aqueous mother liquors with concentrated hydrochloric acid and extraction with chloroform gave no further material.

5.6 The Synthesis of N-Substituted-1-hydroxybenzimidazolin-2-ones

(a) 1-Hydroxy-3-methylbenzimidazolin-2-one (181a)

N-methyl-2-nitroanilinoacetonitrile (168a) (19.1 g; 0.1 mol) was heated under reflux in methanol (100 ml) and a solution of sodium carbonate (5.3 g, 0.05 mol) in water (60 ml) was added dropwise with stirring over 15 min. The dark solution obtained was heated under reflux with stirring for 1.5 h, cooled and evaporated under reduced

pressure. The residue was extracted into chloroform (A) and the extract was washed with water (2 x 20 ml) and evaporated to give a brown gum (4.1 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture and was chromatographed on alumina.

Elution with light petroleum gave N-methyl-2-nitroaniline (167a) (0.53 g) (4%), m.p. 35° (lit. 37°), identical (i.r. spectrum) with an authentic sample.

Elution with light petroleum-toluene (3:1) gave an unidentified intractable brown gum (0.39 g). Further elution with light petroleum-toluene (3:1) gave N-methyl-2-nitroanilinoacetonitrile (168a) (0.19 g) (1%), identical (i.r. spectrum) with an authentic sample.

Elution with toluene followed by ether and chloroform gave several unidentified brown gums (total 0.5 g).

Further elution with chloroform gave (N-methyl-2-nitroanilino)-acetamide (176) as orange prisms (1.0 g) (5%), m.p. 87° (from benzene), ν_{max} 3500-3300 br (NH_2) and 1680-1670 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.49 (1H, d, J 7.5 Hz, ArH), 1.86-2.22 (3H, m, ArH), 2.47 (1H, broad, NH), 2.65 (1H, broad, NH), 5.08 (2H, s, CH_2) and 6.32 (3H, s, $N.CH_3$).

Found: C, 51.6; H, 5.3; N, 20.0%: M^+ 209

$C_{19}H_{11}N_3O_3$ requires: C, 51.7; H, 5.3; N, 20.1%: M 209

Further elution with chloroform gave 1-methylbenzimidazole-2-carboxamide 3-N-oxide (182) as colourless prisms (0.3 g) (2%), m.p. 251° (lit.[17] 251°) (from ethanol-glacial acetic acid), ν_{max} 3250-3150 br (NH_2) and 1690 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 1.84-2.24 (4H, m, ArH) and 5.60 (3H, s, $N.CH_3$).

Found: C, 56.4; H, 4.7; N, 22.2%: M^+ 191

Calculated for $C_9H_9N_3O_2$: C, 56.5; H, 4.7; N, 22.0%: M 191

The aqueous phase was acidified with 5M aqueous hydrochloric acid and extracted with chloroform to afford 1-hydroxy-3-methyl-benzimidazolin-2-one (181a) as colourless prisms (11.0 g) (67%),

m.p. 202° (lit.[17] 207°) (from ethanol), ν_{max} 3200–2600 br (OH) and 1700–1600 br (CO), τ ($CF_3.CO_2H$) 2.54–2.86 (4H, m, ArH) and 6.40 (3H, s, $N.CH_3$).

Found: C, 58.2; H, 4.9; N, 17.0%: M^+ 164

Calculated for $C_8H_8N_2O_2$: C, 58.5: H, 4.9: N, 17.1%: M 164

The hydroxybenzimidazolinones (181a–e) gave dark green colours with ferric chloride in ethanol.[43]

The conditions described in this experiment were used in experiments 5.6(b)–(e).

(b) 1-Hydroxy-3-phenylbenzimidazolin-2-one (181b)

Cyclisation of N-phenyl-2-nitroanilinoacetonitrile (168b) (0.1 mol) gave 1-hydroxy-3-phenylbenzimidazolin-2-one (181b) as colourless plates (15 g) (66%), m.p. 216° (from ethanol), ν_{max} 3400–2600 br (OH) and 1705–1680 br (CO) cm^{-1}, τ ($CF_3.CO_2H$) 2.26–2.96 (m, ArH).

Found: C, 69.5; H, 4.9; N, 12.5%: M^+ 226

$C_{13}H_{10}N_2O_2$ requires: C, 69.0; H, 4.5; N, 12.4%: M 226.

Chloroform (A) gave a brown gum (4.1 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(c) 3-Benzyl-1-hydroxybenzimidazolin-2-one (181c)

Cyclisation of N-benzyl-2-nitroanilinoacetonitrile (168c) (0.1 mol) gave 3-benzyl-1-hydroxybenzimidazolin-2-one (181c) as colourless needles (14.4 g) (60%), m.p. 172° (from ethanol), ν_{max} 3300–2700 br (OH) and 1700–1680 br (CO) cm^{-1}, τ ($CF_3.CO_2H$) 2.42–2.88 (9H, m, ArH) and 4.76 (2H, s, CH_2),

Found: C, 69.7; H, 5.0; N, 11.7%: M^+ 240

$C_{14}H_{12}N_2O_2$ requires: C, 70.0; H, 5.0; N, 11.7%: M 240.

Chloroform (A) gave a brown gum (8.0 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(d) 3-Benzyl-1-hydroxy-5-methylbenzimidazolin-2-one (181d)

Cyclisation of N-benzyl-5-methyl-2-nitroanilinoacetonitrile (168d) (1.40 g, 0.005 mol) gave 3-benzyl-1-hydroxy-5-methylbenzimidazolin-2-one (181d) as cream coloured prisms (0.51 g) (40%), m.p. 171° (from ethanol), ν_{max} 3200-2600 br (OH) and 1700-1660 br (CO) cm^{-1}, τ($CF_3.CO_2H$) 2.60-3.06 (8H, m, ArH), 4.79 (2H, s, CH_2) and 7.63 (3H, s, CH_3).

Found: C, 71.2; H, 5.6; N, 11.1%,

$C_{15}H_{14}N_2O_2$ requires: C, 70.9; H, 5.6; N, 11.0%.

The chloroform extract (A) was washed with saturated aqueous sodium carbonate, and evaporated to give a brown gum (0.55 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

The aqueous sodium carbonate washings were acidified with 5M aqueous hydrochloric acid and extracted with chloroform to give a further crop of the N-hydroxybenzimidazolin-2-one (181d) (0.12 g) (10%), m.p. 168°, identical (i.r. spectrum) with the first crop.

(e) 3-Benzyl-6-chloro-1-hydroxybenzimidazolin-2-one (181e)

Cyclisation of N-benzyl-4-chloro-2-nitroanilinoacetonitrile (168e) (30.1 g, 0.1 mol) gave 3-benzyl-6-chloro-1-hydroxybenzimidazolin-2-one (181e) as colourless rectangular prisms (12.0 g) (44%), m.p. 181° (from ethanol), ν_{max} 2700-2500 br (OH) and 1710-1680 br (CO) cm^{-1}, τ($CF_3.CO_2H$) 2.60-2.06 (8H, m, ArH) and 4.81 (2H, s, CH_2),

Found: C, 61.1; H, 4.1; N, 10.0%

$C_{14}H_{11}ClN_2O_2$ requires: C, 61.2; H, 4.0; N, 10.2%.

The chloroform extract (A) was washed with saturated aqueous sodium carbonate and evaporated to give a brown gum (13.8 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

The aqueous sodium carbonate washings were acidified with 5M

aqueous hydrochloric acid and extracted with chloroform to give a further crop of the N-hydroxybenzimidazolin-2-one (181e) (1.5 g) (5%), m.p. 180°, identical (i.r. spectrum) with the first crop.

The Attempted Cyclisation of N-Benzyl-5-chloro-2-nitroanilino-acetonitrile (168f)

The cyano compound (168f) (3.01 g, 0.01 mol) was heated under reflux in methanol (10 ml) and a solution of sodium carbonate (0.53 g, 0.005 mol) in water (6.0 ml) was added dropwise with stirring over a period of 15 min. The reaction mixture was heated under reflux with stirring for 1.5 h, allowed to cool and evaporated under reduced pressure.

The residue was treated with water and extracted with chloroform to give a brown gum (1.5 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture and gave no solid material on trituration with organic solvents.

The aqueous phase was acidified with concentrated hydrochloric acid and extracted with chloroform to give a dark brown gummy solid (0.23 g) which could not be crystallised.

5.7 The Synthesis of 2-Nitroanilinoacetamide Derivatives

(a) 2-Nitroanilinoacetamide (175)

2-Nitroanilinoacetonitrile (165a) (4.0 g, 0.022 mol) was stirred at 80° in polyphosphoric acid (16 g) for 1.5 h. Ice cold water (50 ml) was added and the mixture was stirred for 0.5 h. The orange solid obtained was collected, washed with water (20 ml) and dried to give 2-nitroanilinoacetamide (175) as orange microcrystalline prisms (3.6 g) (84%), m.p. 181° (from glacial acetic acid) ν_{max} 3500-3200 (NH_2), 1710 (CO), 1530 and 1360 (NO_2) cm^{-1}, τ($CF_3.CO_2H$) 1.56-1.74

(1H, m, ArH), 2.00-2.40 (2H, m, ArH and NH), 2.74-3.00 (2H, m, ArH) and 5.51 (2H, s, CH_2).

Found: C, 49.2; H, 4.9; N, 21.0%

$C_8H_9N_3O_3$ requires: C, 49.2; H, 4.7; N, 21.5%.

(b) 5-Chloro-2-nitroanilinoacetamide (171)

5-Chloro-2-nitroanilinoacetonitrile (165h) (0.4 g, 0.002 mol) was stirred at 80° in polyphosphoric acid (2.0 g) for 3h. Water (10 ml) was added and on scratching, a yellow solid was obtained which was collected and washed with water to give 5-chloro-2-nitroanilinoacetamide (171) as yellow prisms (0.37 g) (81%), m.p. 215° (from ethanol-glacial acetic acid) identical (i.r. spectrum) with a sample obtained previously.

(c) (N-Methyl-2-nitroanilino)acetamide (176)

N-Methyl-2-nitroanilinoacetonitrile (168a) (4.31 g, 0.022 mol) was stirred at 80° in polyphosphoric acid (16 g) for 1.5 h. Water (100 ml) was added and the solution was neutralised by the addition of solid sodium hydrogen carbonate and extracted with chloroform to give (N-methyl-2-nitroanilino)acetamide (176) (3.0 g) (65%), m.p. 86° (from benzene), identical (i.r. spectrum) with a sample obtained before.

(d) (N-Benzyl-2-nitroanilino)acetamide (177)

N-Benzyl-2-nitroanilinoacetonitrile (168c) (2.0 g, 0.0075 mol) was stirred at 80° in polyphosphoric acid (8.0 g) for 3 h. Water (40 ml) was added and the reaction mixture was stirred giving a brown gum. The reaction mixture was extracted with chloroform and the extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to give a brown gum (2.04 g) which was chromatographed on alumina.

Elution with toluene-ether (1:1) gave an unidentified gummy solid (0.47 g) which could not be crystallised from organic solvents.

Elution with chloroform gave (N-benzyl-2-nitroanilino)acetamide (177) as orange prisms (0.48 g) (22%), m.p. 112° (from ethanol), ν_{max} 3450 and 3200 (NH_2), 1630 (CO), 1530 and 1370 (NO_2) cm^{-1}, τ($CF_3.CO_2H$) 1.84 (1H, s, ArH), 1.20-2.04 (10H, m, ArH and NH_2), 5.58 (2H, s, CH_2) and 6.00 (2H, s, CH_2).

Found: C, 66.1; H, 5.4; N, 13.0%: M^+ 285

$C_{15}H_{15}N_3O_3$ requires: C, 63.2; H, 5.3; N, 14.7%: M 285.

Further elution with chloroform gave 2-nitroanilinoacetamide (175) (0.53 g) (36%), m.p. 181° (from ethanol-glacial acetic acid), identical (i.r. spectrum) with a sample obtained previously.

Cyclisation of (N-Methyl-2-nitroanilino)acetamide (176)

(i) (N-Methyl-2-nitroanilino)acetamide (176) (2.09 g, 0.01 mol) was heated under reflux with stirring in methanol (10 ml) and a solution of sodium acetate (0.82 g, 0.01 mol) in water (6.0 ml) was added dropwise over 15 min. The mixture was heated under reflux with stirring for 1.5 h, cooled, diluted with water (20 ml) and extracted with chloroform (A) to give the starting amide (176) (2.05 g) (98%), m.p. 86° (from ethanol), identical (i.r. spectrum) with a sample obtained before.

Acidification of the aqueous mother liquors with 5M aqueous hydrochloric acid yielded no further material.

(ii) Experiment (i) was repeated using sodium carbonate (0.53 g, 0.005 mol) as the base. The chloroform extract (A) gave a brown gum (0.76 g) which on trituration with ether-methanol gave 1-methylbenzimidazole-2-carboxamide 3-N-oxide (182) (0.32 g) (17%), m.p. 251° (from ethanol-glacial acetic acid), identical (i.r. spectrum) with a

sample prepared before. The ether-methanol mother liquors were evaporated to give an unidentified brown gum (0.4 g).

Acidification of the aqueous sodium carbonate mother liquors with 5M aqueous hydrochloric acid and extraction with chloroform gave 1-methylbenzimidazole-2-carboxylic acid 3-N-oxide (184) as cream prisms (0.38 g) (20%), m.p. 248° (from ethanol-glacial acetic acid) (lit.[17] 70°), ν_{max} 2700 br (OH) and 1700-1670 br (CO), τ ($CF_3.CO_2H$) 1.94-2.14 (1H, m, ArH), 2.30-2.48 (3H, m, ArH) and 6.12 (3H, s, $N.CH_3$), M^+ 192 (M 192).

5.8 Benzimidazolin-2-ones

The N-hydroxybenzimidazolin-2-ones (181) were heated under reflux with an equal weight of sodium dithionite in the minimum quantity of 70% v/v aqueous ethanol (50-100 ml) for 1 h. Heating was interrupted, a further portion of sodium dithionite was added and heating under reflux was continued for a further 1 h. The reaction mixture was hot filtered and the filtrate was cooled, evaporated, and the residue was washed with water. The solid was collected, washed with water and dried in vacuo to afford the benzimidazolin-2-ones (188).

(i) 1-Hydroxy-3-methylbenzimidazolin-2-one (181a) (0.33 g, 0.002 mol) gave 3-methylbenzimidazolin-2-one (188a) (0.13 g) (44%), m.p. 195° (lit.[70] 197°), ν_{max} 3200-2800 br (OH, NH) and 1705 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 2.46-2.80 (4H, m, ArH) and 6.36 (3H, s, $N.CH_3$).

(ii) 1-Hydroxy-3-phenylbenzimidazolin-2-one (181b) (0.25 g, 0.0011 mol) gave 3-phenylbenzimidazolin-2-one (188b) (0.16 g) (69%), m.p. 204° (lit.[72] 204°), ν_{max} 3200-2700 br (OH, NH) and 1705-1690 br (CO) cm^{-1}, τ ($CF_3.CO_2H$) 2.30-3.10 (m, ArH).

The product was identical (i.r. spectrum and m.p.) with an authentic sample prepared by the method of Rosnati[72], by cyclisation of diphenylurea using sodium hypochlorite.

(iii) 3-Benzyl-1-hydroxybenzimidazolin-2-one (181c) (0.5 g, 0.002 mol) gave 3-benzylbenzimidazolin-2-one (188c) (0.21 g) (47%), m.p. 195° (from ethanol) (lit.[71] 196°), ν_{max} 3300-2800 br (OH, NH) and 1710-1680 br (CO) cm^{-1}, τ ($CF_3.CO_2H$) 2.46-2.84 (9H, m, ArH) and 4.73 (2H, s, CH_2).

(iv) 3-Benzyl-5-methyl-1-hydroxybenzimidazolin-2-one (181d) (0.38 g, 0.0015 mol) gave 3-benzyl-5-methylbenzimidazolin-2-one (188d) as colourless prisms (0.23 g) (65%), m.p. 251° (from ethanol-glacial acetic acid), ν_{max} 3300-2700 br (OH, NH) and 1700-1690 (CO) cm^{-1}, τ ($CF_3.CO_2H$) 2.60-3.00 (8H, m, ArH), 4.76 (2H, s, CH_2) and 7.61 (3H, s, CH_3).

Found: C, 75.2; H, 6.0; N, 11.4%

$C_{15}H_{14}N_2O$ requires: C, 75.6; H, 5.9; N, 11.8%.

(v) 3-Benzyl-6-chloro-1-hydroxybenzimidazolin-2-one (181e) (0.5 g, 0.0018 mol) gave 3-benzyl-6-chlorobenzimidazolin-2-one (188e) (0.3 g) (65%), m.p. 175° (from ethanol) (lit.[73] 176°), ν_{max} 3400 br (OH, NH) and 1710-1700 (CO) cm^{-1}.

5.9 Reactions of 1-Hydroxybenzimidazolin-2-ones

(a) Reactions of 1-Hydroxybenzimidazolin-2-ones (181) with Acetic Anhydride under Mild Conditions

A suspension of the benzimidazolinone (181) (0.006 mol) was stirred at room temperature in acetic anhydride (0.9 ml, 0.009 mol) for 22 h. Water (3.0 ml) was added and the mixture was stirred at room temperature for 1 - 2 h. The colourless solid was collected by

filtration (A), washed with water and dried in vacuo.

In the cases (B) where no solid was obtained after stirring for 2 h with water, the reaction mixture was extracted with ether. The extract was washed with saturated aqueous sodium hydrogen carbonate solution, and evaporated to yield the product.

The quantities described above were used in experiements 5.9(a)(i)-(iv).

(i) 1-Acetoxy-3-methylbenzimidazolin-2-one (190a) was prepared from 1-Hydroxy-3-methylbenzimidazolin-2-one (181a) as colourless prisms (1.21 g) (98%), m.p. 120° (from benzene), ν_{max} 1790 (cyclic N.OAc) and 1720 (CO) cm^{-1}, τ ($CDCl_3$) 2.68-3.14 (4H, m, ArH), 6.60 (3H, s, $N.CH_3$) and 7.62 (3H, s, N.OAc).

Found: C, 58.1; H, 4.9; N, 13.6%: M^+ 206

$C_{10}H_{10}N_2O_3$ requires: C, 58.2; H, 4.9; N, 13.6%: M 206.

(ii) 1-Acetoxy-3-benzylbenzimidazolin-2-one (190b) was prepared from 3-Benzyl-1-hydroxybenzimidazolin-2-one (181c) as colourless prisms (94%), m.p. 106° (from benzene), ν_{max} 1805 (cyclic N.OAc) and 1730-1710 (CO) cm^{-1}, τ ($CDCl_3$) 2.60-3.20 (9H, m, ArH), 4.94 (2H, s, CH_2) and 7.62 (3H, s, N.OAc).

Found: C, 68.1; H, 5.0; N, 9.9%: M^+ 282

$C_{16}H_{14}N_2O_3$ requires: C, 68.0; H, 5.0; N, 9.7%: M 282.

(iii) 3-Benzyl-1-hydroxy-5-methylbenzimidazolin-2-one (181d) gave a gummy solid which was extracted into ether (B) to give 1-acetoxy-3-benzyl-5-methylbenzimidazolin-2-one (190c) as colourless prisms (86%), m.p. 135° (from benzene), ν_{max} 1810 (cyclic N.OAc) and 1750-1690 br (CO) cm^{-1}.

Found: C, 69.0; H, 5.5; N, 9.3%

$C_{17}H_{16}N_2O_3$ requires: C, 68.9; H, 5.4; N, 9.4%.

(iv) 1-Hydroxy-3-phenylbenzimidazolin-2-one (181b) gave a clear gum which on trituration with water (3.0 ml) failed to produce any solid material and on standing became dark brown and intractable.

(b) Reactions of 1-Hydroxybenzimidazolin-2-ones with Hot Acetic Anhydride

(i) 3-Benzyl-1-hydroxybenzimidazolin-2-one (181c) (0.24 g, 0.001 mol) was treated with the minimum quantity of acetic anhydride (0.6 ml, 0.006 mol) and the mixture was heated at 100° in a boiling water bath. The mixture became dark green and after ca. 1 min an exothermic reaction took place causing the acetic anhydride to boil. The dark brown solution was heated at 100° for 10 min, allowed to stand at room temperature for 20 min and evaporated. The residue was triturated with ether to give 5-acetoxy-3-benzylbenzimidazolin-2-one (196b) (0.12 g) (41%), m.p. 207° (from ethanol), identical (i.r. spectrum) with a sample obtained previously.

The ether mother liquors were evaporated to give a brown intractable gum (0.1 g). The conditions and quantities described in this experiment were used in experiments 5.9(b)(ii) and (iii).

(ii) 1-Hydroxy-3-phenylbenzimidazolin-2-one (181b) was treated with acetic anhydride as described in experiment 5.9(b)(i) to give a gummy solid (0.3 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture which could not be crystallised from organic solvents.

(iii) 3-Benzyl-1-hydroxy-5-methylbenzimidazolin-2-one (181d) was treated with acetic anhydride as described in experiment 5.9(b)(i) to give a gum (0.20 g) which on trituration with ether gave a semi-solid (0.10 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

The ether mother liquors were evaporated to give a gum (0.09 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(iv) 1-Hydroxy-3-methylbenzimidazolin-2-one (181a) (0.98 g, 0.006 mol) was treated with acetic anhydride (0.9 ml, 0.009 mol) and the suspension was stirred in a water bath at 50°. The temperature of the water bath was slowly increased to 100° over a period of 1.25 h during which time the solid slowly dissolved giving a pale brown solution. The temperature was maintained at 100° for 5 min and then the reaction mixture was cooled and evaporated to give a brown gum. Trituration of the gum with ether-ethanol gave a solid (0.66 g), m.p. 195°, ν_{max} 1750-1680 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 2.40-3.40 (9 units, m, ArH), 6.40-6.80 (14 units, m, $N.CH_3$) and 7.76 (3 units, d, J 2.5 Hz, O.Ac), identical [i.r. and ^1H n.m.r. spectrum ($CF_3.CO_2H$)] with the product obtained by heating the N-acetoxybenzimidazolinone (190a) in toluene (page 200). Attempts to crystallise the solid from glacial acetic acid or ethanol-glacial acetic acid resulted in the formation of an intractable gelatinous precipitate. The solid was unchanged (identical i.r. spectrum) after trituration with saturated aqueous sodium hydrogen carbonate, and gave no colour with ferric chloride in ethanol.

The ether-ethanol mother liquors were evaporated to give 6-acetoxy-1-methylbenzimidazolin-2-one (196a) (0.28 g) (23%), m.p. 199° (from ethanol), identical (i.r. spectrum) with a sample obtained before.

(c) The Attempted Reaction of 1-Hydroxy-3-methylbenzimidazolin-2-one (181a) with Acetic Anhydride in the Presence of Concentrated Sulphuric Acid

The 1-hydroxybenzimidazolinone (181a) (0.5 g) (0.003 mol) was treated with acetic anhydride (0.5 ml, 0.005 mol) at room temperature and one drop of concentrated sulphuric acid was added. A vigorous exothermic reaction took place and a dark brown solution was obtained which was allowed to stand at room temperature for 20 min. The reaction mixture was evaporated to give an intractable black tar (0.5 g) from which no solid could be obtained.

(d) The Acetylation of 2-Cyano-1-hydroxybenzimidazole (178a)

(i) The benzimidazole (178a) (0.53 g, 0.0033 mol) was heated under reflux with acetyl chloride (7.5 ml) in glacial acetic acid (7.5 ml) for 2 h. The reaction mixture was cooled and evaporated to give 1-acetoxy-2-cyanobenzimidazole (197) as a colourless solid, (0.67 g) (100%), m.p. 83°, ν_{max} 2220 (CN) and 1815 (cyclic N.OAc) cm^{-1}. On attempted crystallisation from ethanol, the N-acetoxy compound (197) was hydrolysed to 2-cyano-1-hydroxybenzimidazole (178a) identical (i.r. spectrum) with an authentic sample.

(ii) The benzimidazole (178a) (1.59 g, 0.1 mol) was heated under reflux in acetic anhydride (5.0 ml) for 3 h. The reaction mixture was cooled and evaporated to give the starting benzimidazole (178a) (1.58 g) (99%), m.p. 225°, identical (i.r. spectrum) with an authentic sample. A small amount (0.01 g) of the N-acetoxy compound (197), m.p. 82°, ν_{max} 2220 (CN) and 1815 (cyclic N.OAc) cm^{-1} was recovered from the gland of the rotary evaporator, and was identical (i.r. spectrum) with the N-acetoxy compound (197) obtained before.

(e) Reactions of 1-Hydroxybenzimidazolin-2-ones with Acetyl Chloride

(i) 1-Hydroxy-3-methylbenzimidazolin-2-one (181a) (0.17 g, 0.001 mol) was heated under reflux with acetyl chloride (2.5 ml) in glacial acetic acid (2.5 ml) for 2 h. The reaction mixture was cooled and evaporated to yield 1-acetyl-5-chloro-3-methylbenzimidazolin-2-one (196c) as colourless prisms (0.18 g) (80%), m.p. 174° (from ethanol), ν_{max} 1740-1700 br (N.Ac and CO) cm^{-1}, τ ($CDCl_3$) 1.92 (1H, d, J_{ortho} 8.5 Hz, H-7), 2.90 (1H, dd, J_{ortho} 8.5 Hz, J_{meta} 2.5 Hz, H-6), 3.06 (1H, d, J_{meta} 2.5 Hz, H-4), 6.66 (3H, s, N.CH_3) and 7.28 (3H, s, N.Ac).

Found: C, 53.4; H, 4.0; N, 12.5%

$C_{10}H_9ClN_2O_2$ requires: C, 53.4; H, 4.0; N, 12.5%.

The conditions and quantities used in this experiment were used in experiments 5.9(e)(ii)-(iv).

(ii) 1-Hydroxy-3-phenylbenzimidazolin-2-one (181b) afforded 1-acetyl-5-chloro-3-phenylbenzimidazolin-2-one (196d) as colourless prisms (100%), m.p. 150° (from ethanol), ν_{max} 1740 (N.Ac) and 1705 (CO) cm^{-1}, τ ($CDCl_3$) 1.81 (1H, d, J_{ortho} 8.5 Hz, H-7), 2.40-2.60 (5H, m, ArH), 2.84 (1H, dd, J_{ortho} 8.5 Hz, J_{meta} 2.5 Hz, H-6), 3.05 (1H, d, J_{meta} 2.5 Hz, H-4) and 7.22 (3H, s, N.Ac).

Found: C, 63.0; H, 3.8; N, 9.9%: M^+ 286 (288)

$C_{15}H_{11}ClN_2O_2$ requires: C, 62.8; H, 3.8; N, 9.8%: M 286.5.

(iii) 3-Benzyl-1-hydroxybenzimidazolin-2-one (181c) gave 1-acetyl-3-benzyl-5-chlorobenzimidazolin-2-one (196e) as colourless needles (100%), m.p. 124° (from ethanol), ν_{max} 1735 (N.Ac) and 1705 (CO) cm^{-1}, τ ($CDCl_3$) 1.93 (1H, d, J_{ortho} 8.5 Hz, H-7), 2.71 (5H, s, ArH), 2.96 (1H, dd, J_{ortho} 8.5 Hz, J_{meta} 2.5 Hz, H-6), 3.17 (1H, d, J_{meta} 2.5 Hz, H-4), 5.02 (2H, s, CH_2) and 7.24 (3H, s, N.Ac).

Found: C, 63.6; H, 4.3; N, 9.3%: M^+ 300 (302)

$C_{16}H_{13}ClN_2O_2$ requires: C, 63.9; H, 4.3; N, 9.3%: M 300.5.

(iv) 3-Benzyl-1-hydroxy-5-methylbenzimidazolin-2-one (181d) gave 1-acetyl-3-benzyl-6-chloro-5-methylbenzimidazolin-2-one (196f) (99%), m.p. 115° (from ethanol), ν_{max} 1740 (N.Ac) and 1700 (CO) cm^{-1}; τ ($CDCl_3$) 1.78 (1H, s, H-7), 2.60-2.80 (5H, m, ArH), 3.28 (1H, s, H-4), 4.99 (2H, s, CH_2), 7.23 (3H, s, N.Ac) and 7.66 (3H, s, CH_3), M^+ 314 (316), (M 314.5).

On crystallisation from ethanol-glacial acetic acid, the compound was deacetylated to afford 3-benzyl-6-chloro-5-methylbenzimidazolin-2-one (196g) as colourless prisms m.p. 251°.

Found: C, 66.4; H, 4.8; N, 10.4%: M^+ 272 (273)

$C_{15}H_{13}ClN_2O$ requires: C, 66.1; H, 4.8; N, 10.3%: M 272.5.

(f) Reactions of 1-Hydroxybenzimidazolin-2-ones with Acetyl Bromide

(i) 1-Hydroxy-3-methylbenzimidazolin-2-one (181a) (0.16 g) (0.001 mol) was heated under reflux with acetyl bromide (2.5 ml) in glacial acetic acid (5.0 ml) for 2 h. The reaction mixture was cooled and evaporated to give a clear gum (0.18 g) which on trituration with ether gave 1-acetyl-5-bromo-3-methylbenzimidazolin-2-one (196h) as cream coloured prisms (0.08 g) (31%), m.p. 169° (from ethanol-glacial acetic acid), ν_{max} 1760-1700 (CO) cm^{-1}, τ ($CDCl_3$) 1.98 (1H, d, J_{ortho} 8.0 Hz, H-7), 2.77 (1H, dd, J_{ortho} 8.0 Hz, J_{meta} 2.5 Hz, H-6), 2.92 (1H, d, J_{meta} 2.5 Hz, H-4), 6.66 (3H, s, $N.CH_3$) and 7.28 (3H, s, N.Ac).

Found: C, 44.7; H, 3.3; N, 10.3%: M^+ 268 (270)

$C_{10}H_9BrN_2O_2$ requires: C, 44.6; H, 3.3; N, 10.4%: M 269.

The ether mother liquors were evaporated to give a clear gum (0.09 g) which was shown by t.l.c. (chloroform) to be a

multicomponent mixture. Trituration with organic solvents or with saturated aqueous sodium hydrogen carbonate failed to produce any further solid.

The conditions and quantities described in this reaction were used in reactions 5.9(f)(ii) and (iii).

(ii) 1-Hydroxy-3-phenylbenzimidazolin-2-one (181b) gave a colourless semi-solid (0.34 g), ν_{max} 1750-1720 br (CO), τ ($CDCl_3$) 1.86 (1 unit, d, J_{ortho} 8.0 Hz, ArH), 2.30-3.10 (13 units, m, ArH), 7.24 (3 units, s, N.Ac). The integration of the ^1H n.m.r. spectrum indicated that the solid was a mixture. This was also shown by the t.l.c. (chloroform) of the solid which showed that it was a two component mixture.

The solid (0.3 g) was dissolved in the minimum quanitty of hot acetic anhydride (0.5 ml) and the solution was heated in a boiling water bath for 5 min, cooled and evaporated to give a colourless solid (0.28 g) m.p. 120-185°, ν_{max} 1740-1700 br (CO) cm^{-1}. The integration of the ^1H n.m.r. spectrum and the t.l.c. (chloroform) of the solid indicated that it was a two component mixture. Attempts to crystallise the solid from organic solvents were unsuccessful.

(iii) 3-Benzyl-1-hydroxybenzimidazolin-2-one (181c) gave a colourless semi-solid (0.3 g) which solidified on trituration with ether to give a colourless solid (0.1 g) m.p. 120-165°, ν_{max} 1740-1700 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.04 (1 unit, d, J_{ortho} 8.0 Hz, ArH), 2.50-3.20 (11 units, m, ArH), 4.90 (2 units, s, CH_2), 4.99 (1 unit, s, CH_2) and 7.34 (3H, s, N.Ac). The ratio of the signals due to the methylene groups indicated a 2:1 mixture and the t.l.c. (chloroform) of the solid showed the presence of three components. Crystallisation from ethanol failed to effect purification of the solid.

The ether mother liquors were evaporated to give a colourless solid (0.1 g), which was shown by t.l.c. (chloroform) to be a

multicomponent mixture.

(g) Reactions of 1-Hydroxybenzimidazolin-2-ones with Benzoyl Chloride

(i) 1-Benzoyloxy-3-benzylbenzimidazolin-2-one (196m).

3-Benzyl-1-hydroxybenzimidazolin-2-one (181c) (0.48 g, 0.002 mol) was treated with 2M aqueous sodium hydroxide (40 ml) giving a suspension of its sodium salt. Benzoyl chloride (0.73 g, 0.6 ml, 0.005 mol) was added, and the mixture was shaken vigorously at room temperature for 1 h. The colourless solid was collected and washed with water to give the 1-benzoyloxybenzimidazolin-2-one (196m) as colourless needles (0.50 g) (73%), m.p. 256° (from ethanol), ν_{max} 1770 (N.O.CO.Ph) and 1740 (CO) cm^{-1}, τ ($CDCl_3$) 1.66-1.88 (2H, m, ArH), 2.20-3.20 (12H, m, ArH) and 4.89 (2H, s, CH_2).

Found: C, 73.0; H, 4.7; N, 8.0%: M^+ 344

$C_{21}H_{16}N_2O_3$ requires: C, 73.2; H, 4.7; N, 8.1%: M 344.

(ii) 5-Benzoyloxy-3-phenylbenzimidazolin-2-one (196n)

1-Hydroxy-3-phenylbenzimidazolin-2-one (181b) (0.45 g, 0.002 mol) was treated with 2M aqueous sodium hydroxide (20 ml) giving a suspension of the sodium salt. Benzoyl chloride (0.36 g, 0.3 ml, 0.0026 mol) was added and the mixture was shaken vigorously at room temperature for 1 h. The gummy solid obtained was washed with water by decantation and dissolved in ethanol (10 ml). The mixture was heated under reflux for 15 min, cooled and evaporated to give a residue which smelled of ethyl benzoate. Toluene was added and the mixture was evaporated under reduced pressure until the ethyl benzoate had been removed. The gummy residue was crystallised from ethanol-glacial acetic acid to give the 5-benzoyloxy compound (196n) as cream coloured prisms (0.35 g) (53%), m.p. 265°, ν_{max} 3200-2800 br (OH) and 1720 (CO) cm^{-1}, τ($CF_3.CO_2H$) 1.66-1.84 (2H, m, ArH),

2.20-2.60 (9H, m, ArH), 2.78 (1H, dd, J_{ortho} 8.0 Hz, J_{meta} 2.5 Hz, H-6) and 2.98 (1H, d, J_{meta} 2.5 Hz, H-4).

Found: C, 73.1; H, 4.3; N, 8.9%: M^+ 330

$C_{20}H_{14}N_2O_3$ requires: C, 72.7; H, 4.3; N, 8.5%: M 330.

Evaporation of the ethanol mother liquors gave an intractable gum (0.1 g) which failed to yield any solid material on trituration with organic solvents.

(h) Reactions of 1-Hydroxybenzimidazolin-2-ones in the Presence of Toluene-p-sulphonyl Chloride

(i) 1-Hydroxy-3-methylbenzimidazolin-2-one (181a)

A solution of the N-hydroxybenzimidazolinone (181a) (1.23 g, 0.0075 mol) in redistilled pyridine (10 ml) was treated at room temperature with toluene-p-sulphonyl chloride (1.71 g, 0.009 mol). An exothermic reaction took place and a crystalline solid began to separate from the solution. The reaction mixture was stirred at room temperature for 15 h and the solid was collected and washed with ether to give 1-(3-methyl-2-oxobenzimidazolin-5-yl)pyridinium chloride (202) as cream coloured prisms (1.05 g) (54%), m.p. 320-330° (decomp.) (from ethanol), ν_{max} 3350 br (OH, NH), 1690-1680 (CO) cm^{-1}, τ (D_2O) 0.74-0.90 (2H, m, ArH), 1.08-1.30 (1H, m, ArH), 1.58-1.80 (2H, m, ArH), 2.56-2.70 (3H, m, ArH) and 6.65 (3H, s, $N.CH_3$).

^1H n.m.r. internal standard: the sodium salt of 3-(trimethylsilyl)-propane sulphonic acid.

Found: C, 52.8; H, 5.0; N, 14.1%: M^+ 226

$C_{13}H_{12}ClN_3O$ requires: C, 59.7; H, 4.6; N, 16.1%: M 261.5

M (cation) 226

The mother liquors were evaporated to give a brown intractable gum (1.0 g) which was shown by t.l.c. (chloroform) to be a

multicomponent mixture.

The pyridinium salt (202) (0.1 g) was dissolved in 5M aqueous hydrochloric acid giving a pale yellow solution. The acidic solution was extracted with chloroform but no colour was extracted into the chloroform.

The pyridinium salt (202) (0.1 g) was dissolved in 5M aqueous hydrochloric acid (1.0 ml) and the pale yellow solution was basified with 5M aqueous sodium hydroxide giving a deep yellow solution. The basic solution was extracted with chloroform but no colour was extracted into the chloroform.

A solution of the pyridinium salt in water (1.0 ml) was treated with silver nitrate solution (0.5 ml) giving a white precipitate.

A solution of the benzimidazolinone (188a) (0.1 g) in ethanol was treated with ethanolic silver nitrate. No precipitate was obtained.

(ii) 3-Benzyl-1-hydroxy-5-methylbenzimidazolin-2-one (181d)

A solution of the N-hydroxybenzimidazolinone (181d) (0.64 g, 0.0025 mol) in redistilled pyridine (5.0 ml) was stirred in an ice bath and treated with toluene-p-sulphonyl chloride (0.57 g, 0.003 mol). The brown solution was stirred at room temperature for 15 h and evaporated to give a brown gum (0.81 g) which failed to give any solid material on trituration with organic solvents or with water. The gum was dissolved in chloroform and the extract was washed with water and evaporated to give a brown gum (0.55 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture. Trituration with organic solvents failed to produce any solid. The gum was redissolved in chloroform and the extract was washed with 5M aqueous sulphuric acid and evaporated to give a brown gum (0.4 g). Trituration with

organic solvents failed to produce any solid material.

(iii) A solution of 1-hydroxy-3-methylbenzimidazolin-2-one (181a) (0.33 g, 0.002 mol) in 10% w/v aqueous sodium hydroxide solution (5.0 ml) was treated with stirring with toluene-p-sulphonyl chloride (0.42 g, 0.0022 mol). The reaction mixture was stirred at room temperature for 1 h, cooled in an ice bath and acidified with 5M aqueous hydrochloric acid. A black tar was obtained which was extracted into chloroform. The extract was washed with water and evaporated to give a brown intractable gum (0.35 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture. Trituration with organic solvents failed to produce any solid material.

(iv) A solution of the N-hydroxybenzimidazolinone (181a) (0.33 g, 0.002 mol) in chloroform (15 ml) was treated at room temperature with toluene-p-sulphonyl chloride (0.38 g, 0.002 mol). The solution was heated under reflux for 10 min, cooled and evaporated to give a colourless solid which on trituration with ether gave a quantitative yield of the starting N-hydroxybenzimidazolinone (181a), m.p. 200°, identical (i.r. spectrum) with an authentic sample.

The Attempted Clearage of the Pyridinium Salt (202)

The salt (202) (0.52 g, 0.002 mol) was heated under reflux in methanol (10 ml) containing piperidine (5.0 ml) for 3 h. The reaction mixture was cooled, evaporated and extracted with chloroform. The chloroform extract was washed with 5M aqueous hydrochloric acid and evaporated to yield a black intractable gum (0.5 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture. Trituration with organic solvents failed to produce any solid material.

The acidic washings were taken to pH 7 by the addition of 1M

aqueous sodium hydroxide solution and extracted with chloroform. Evaporation of the chloroform yielded no material. The aqueous phase was basified with 1M aqueous sodium hydroxide solution and extracted with chloroform. No material was obtained on evaporation of the chloroform extract.

(i) The Attempted Reaction of 1-Hydroxy-3-methylbenzimidazolin-2-one (181a) with Phosphorus Oxychloride

(i) A solution of the N-hydroxybenzimidazolinone (181a) (0.49 g, 0.003 mol) in chloroform (50 ml) was cooled in an ice bath and treated dropwise with stirring with a solution of phosphorus oxychloride (0.41 ml, 0.0045 mol) in chloroform (2.0 ml). The reaction mixture was heated under reflux for 4 h, cooled and evaporated. The residue was treated with ice (2.0 g), neutralised with saturated aqueous sodium hydrogen carbonate solution and extracted with chloroform to give a pale brown solid (0.95 g) which was contaminated with triethylphosphate, i.r. spectrum identical with an authentic sample. The solid was washed with ether to afford the N-hydroxybenzimidazolinone (181a) (0.48 g) (98%) m.p. 201°, identical (i.r. spectrum) with the starting material.

(ii) A solution of the 1-hydroxybenzimidazolin-2-one (181a) (0.49 g, 0.003 mol) in 1,2-dichloroethane (50 ml) was treated with phosphorus oxychloride (0.68 ml, 0.0075 mol) as described in the previous experiment to give a brown gum (0.19 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture. Trituration with organic solvents failed to produce any solid material. The aqueous sodium hydrogen carbonate washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform but no further material was obtained.

5.10 Reactions of 1-Acetoxy-3-substituted benzimidazolin-2-ones

(a) Reactions in Ethanol

(i) 1-Acetoxy-3-methylbenzimidazolin-2-one (190a) (0.5 g) was heated under reflux in ethanol (5.0 ml) for 2 h. The solution was allowed to cool and the solid which crystallised from the ethanol was collected, washed with water and dried in vacuo to yield 5-acetoxy-3-methylbenzimidazolin-2-one (196a) as cream coloured prisms (0.26 g) (52%), m.p. 199° (from ethanol), ν_{max} 1750 (C.OAc) and 1690 (CO) cm^{-1}, τ [$(CD_3)_2CO$] 3.02 (1H, d, J_{ortho} 8.0 Hz, H-7), 3.18 (1H, d, J_{meta} 2.0 Hz, H-4), 3.32 (1H, dd, J_{ortho} 8.0 Hz, J_{meta} 2.0 Hz, H-6), 6.72 (3H, s, $N.CH_3$) and 7.80 (3H, s, OAc).

Found: C, 58.3; H, 4.9; N, 13.9%: M^+ 206

$C_{10}H_{10}N_2O_3$ requires: C, 58.3; H, 4.9; N, 13.6%: M 206.

The ethanol mother liquors were evaporated to give a brown intractable gum (0.23 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture. Trituration with organic solvents failed to produce any further solid.

(ii) 1-Acetoxy-3-benzylbenzimidazolin-2-one (190b) (0.5 g) was heated in ethanol as described in reaction 5.10(a)(i) to give a colourless solid more of which was obtained by evaporation of the ethanol mother liquors. Crystallisation from ethanol afforded 5-acetoxy-3-benzylbenzimidazolin-2-one (196b) as colourless elongated prisms (0.48 g) (96%), m.p. 208°, ν_{max} 1755 (C.OAc) and 1710-1670 (CO) cm^{-1}, τ [$(CD_3)_2SO$] 2.73 (5H, s, ArH), 3.02 (1H, d, J_{ortho} 8.5 Hz, H-7), 3.13 (1H, d, J_{meta} 2.0 Hz, H-4), 3.30 (1H, dd, J_{ortho} 8.5 Hz, J_{meta} 2.0 Hz, H-6), 5.04 (2H, s, CH_2) and 7.81 (3H, s, O.Ac).

Found: C, 67.6; H, 5.0; N, 9.9%: M^+ 282

$C_{16}H_{14}N_2O_3$ requires: C, 68.1; H, 5.0; N, 9.9%: M 282.

(iii) 1-Acetoxy-3-benzyl-5-methylbenzimidazolin-2-one (190c) (0.5 g) was heated in ethanol as described in reaction 5.10(a)(i) to give 6-acetoxy-3-benzyl-5-methylbenzimidazolin-2-one (196n) as colourless elongated prisms (0.12 g) (24%), m.p. 185° (from ethanol), ν_{max} 1740 (C.OAc) and 1690-80 (CO) cm^{-1}, τ $[(CD_3)_2SO]$ 2.72 (5H, s, ArH), 3.10 (1H, s, ArH), 3.28 (1H, s, ArH), 5.04 (2H, s, CH_2), 7.76 (3H, s, OAc) and 7.96 (3H, s, CH_3).

Found: C, 69.3; H, 5.6; N, 9.5%

$C_{17}H_{16}N_2O_3$ requires: C, 68.9; H, 5.4; N, 9.5%.

The ethanol mother liquors on evaporation gave a brown gum (0.27 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture. Trituration with organic solvents failed to produce any further solid material.

(b) Reaction in Benzene

1-Acetoxy-3-methylbenzimidazolin-2-one (190a) (0.5 g) was heated under reflux in benzene (4.0 ml) for 1 h. The reaction mixture was evaporated to give the starting N-acetoxy compound (181a) (0.5 g, m.p. 118°, identical (i.r. spectrum) with the starting material.

(c) Reaction in Toluene

1-Acetoxy-3-methylbenzimidazolin-2-one (190a) (0.47 g) was heated under reflux in toluene (7.0 ml). The amount of insoluble material present increased with time and after 1 h the t.l.c. (chloroform) of the reaction mixture indicated that the starting material had been entirely consumed. The insoluble material was collected to give an unidentified cream coloured solid (0.17 g), m.p. 185-195°, ν_{max} 1740-1700 br (CO) cm^{-1}, τ ($CF_3.CO_2H$) 2.26-3.06 (2 units, m, ArH), 6.20-6.46 (2 units, m, $N.CH_3$) and 7.56 (1 unit, d, 2.5 Hz, O.Ac).

The doublet at τ7.56 was irradiated but there was no

observable change in the spectrum.

Attempts to crystallise the solid were unsuccessful. With ethanol and with glacial acetic acid a gelatinous precipitate was obtained.

The toluene mother liquors were evaporated to give 5-acetoxy-3-methylbenzimidazolin-2-one (196a) (0.28 g) (59%), m.p. 197°, identical (i.r. spectrum) with an authentic sample.

(d) Reaction in Glacial Acetic Acid

1-Acetoxy-3-methylbenzimidazolin-2-one (190a) (0.5 g) was heated in glacial acetic acid (1.0 ml). The initially colourless solution slowly darkened as the temperature was raised and an exothermic reaction took place. The reaction mixture was heated under reflux for 0.5 h, cooled and evaporated to yield a brown gum (0.5 g) which on trituration with ether-methanol gave 5-acetoxy-3-methylbenzimidazolin-2-one (196a) (0.40 g) (80%), m.p. 196° (from ethanol), identical (i.r. spectrum) with a sample obtained previously.

The mother liquors were evaporated to give a brown intractable gum (0.06 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture.

(e) Reaction with Sodium Acetate in Glacial Acetic Acid

A solution of 1-acetoxy-3-methylbenzimidazolin-2-one (190a) (0.41 g, 0.002 mol) in glacial acetic acid was treated dropwise with stirring at room temperature with a solution of fused sodium acetate (0.35 g, 0.004 mol) in glacial acetic acid (5.0 ml).

The colourless solution was stirred at room temperature for 2 h and then evaporated under reduced pressure using a hot water bath. As the temperature of the water bath increased, the colourless solution became dark brown. The gummy residue obtained was extracted into

chloroform. The extract was washed with saturated aqueous sodium hydrogen carbonate, and evaporated to give a brown gum (0.34 g) which on trituration with ether-methanol gave 5-acetoxy-3-methylbenzimidazolin-2-one (196a) (0.15 g) (36%), m.p. 197° (from ethanol), identical (i.r. spectrum) with a sample obtained previously.

The ether-methanol mother liquors were evaporated to give an intractable brown gum (0.18 g) which was shown by t.l.c. (chloroform) to be a multicomponent mixture. Trituration with organic solvents failed to produce any solid.

The aqueous sodium hydrogen carbonate washings were acidified with 5M aqueous sulphuric acid and extracted with chloroform to give an intractable brown gum (0.02 g).

(f) The Reaction of 1-Acetoxy-3-methylbenzimidazolin-2-one (190a) with Propionic Acid

1-Acetoxy-3-methylbenzimidazolin-2-one (190a) (0.5 g, 0.0025 mol) was warmed in propionic acid (1.0 ml). As the temperature was raised, an exothermic reaction took place and the reaction mixture boiled and became dark brown. The reaction mixture was heated under reflux for 15 min, cooled and the residue was triturated with ethanol-ether to give a solid (0.15 g), τ ($CF_3.CO_2H$) (60 Mhz ^1H n.m.r. spectrum) 2.40-3.13 (5 units, m, ArH), 4.44 (5 units, s, $N.CH_3$), 7.25 (2 units, q, J 7.0 Hz, CH_2), 7.52 (1 unit, s, OAc) and 8.63 (3 units, t, CH_3).

The ^1H n.m.r. spectrum indicated that the solid was a mixture of the 5-acetoxy and the 5-propionyloxy compound in the ratio 1:3 respectively. The mixture crystallised unchanged (identical i.r. spectrum) from ethanol-glacial acetic acid.

(g) The Attempted Reaction of 1-Acetoxy-3-methylbenzimidazolin-2-one (190a) with Acetic Anhydride

A suspension of 1-acetoxy-3-methylbenzimidazolin-2-one (190a) (0.41 g, 0.002 mol) in acetic anhydride (0.25 ml, 0.0025 mol) was heated in a water bath at 85° for 10 min, and then at 100° for 5 min. A pale brown solution was obtained which on cooling deposited a cream coloured solid. This was collected, washed with water and dried to yield the starting 1-acetoxybenzimidazolinone (190a) (0.38 g) (93%), m.p. 116°, identical (i.r. spectrum) with the starting material.

(h) The Attempted Reaction of 1-Acetoxy-3-methylbenzimidazolin-2-one (190a) with Sodium Cyanide in Ethanol

(i) A solution of 1-acetoxy-3-methylbenzimidazolin-2-one (190a) (0.41 g, 0.002 mol) in ethanol (25 ml) was treated at room temperature with a solution of sodium cyanide (0.1 g, 0.002 mol) in water (1.0 ml). The colourless solution was stirred at room temperature for 2 h and evaporated at room temperature. The residue was dissolved in water, and the solution was acidified with 5M aqueous hydrochloric acid to give a colourless precipitate which was collected, washed with water and dried *in vacuo* to afford 1-hydroxy-3-methylbenzimidazolin-2-one (181a) (0.31 g) (95%), m.p. 201°, identical (i.r. spectrum) with a sample obtained previously.

(ii) A solution of 1-acetoxy-3-methylbenzimidazolin-2-one (190a) (0.41 g, 0.002 mol) in warm ethanol (5.0 ml) was treated with a solution of sodium cyanide (0.2 g, 0.004 mol) in water (1.0 ml). The solution was heated under reflux for 1 h and then allowed to cool. The solid which crystallised out was collected, washed with ethanol (1.0 ml) and dissolved in water (2.0 ml). Acidification

with 5M aqueous hydrochloric acid gave a cream coloured precipitate which was collected, washed with water and dried *in vacuo* to yield 1-hydroxy-3-methylbenzimidazolin-2-one (181a) (0.15 g) (46%), m.p. 201°, identical (i.r. spectrum) with a sample obtained previously.

The ethanol mother liquors were evaporated and the residue was dissolved in water. Acidification with 5M aqueous hydrochloric acid gave a further crop of 1-hydroxy-3-methylbenzimidazolin-2-one (181a) (0.13 g) (40%), m.p. 200°, identical (i.r. spectrum) with the first crop.

Appendix

Experimental Notes

Infra red spectra were measured for nujol suspensions or thin films using a Pye-Unicam S.P. 200 Spectrophotometer; bands were either strong or very strong unless otherwise specified (w) as weak or (br) broad.

Nuclear magnetic resonance spectra (^{1}H n.m.r.) were measured at 100 Mhz using a Varian HA 100 instrument. The temperature used was 28° and tetramethylsilane was used as internal standard. Chemical shifts are given in τ values, s = singlet, d = doublet, dd = double doublet, m = multiplet, q = quartet and t = triplet.

Mass spectra were measured at 800 Kv on an A.E.I. MS 902 instrument.

Microanalyses were carried out by Alfred Bernhardt, West Germany, the National Physical Laboratory and by Mr. Brian Clark and Mr. John Grunbaum, Department of Chemistry, University of Edinburgh. Melting points (uncorrected) of all analytical samples were determined on a Kofler block.

Thin layer chromatography (t.l.c.) was carried out over silica and the solvent which was used is specified in each case. The t.l.c. silica was Kieselgel $C.F._{254}$ nach Stahl.

Column chromatography was carried out over 5% deactivated alumina (Spence type H).

Solvents were of technical grade and light petroleum had boiling point 60-80°.

Extracts of organic solvents were washed with water and dried over $MgSO_4$ prior to evaporation under reduced pressure.

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Publications

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lovel substitution reactions of 1-*N*-acetoxy-3,4-dihydro--oxo-2-phenylquinoxalinium perchlorates

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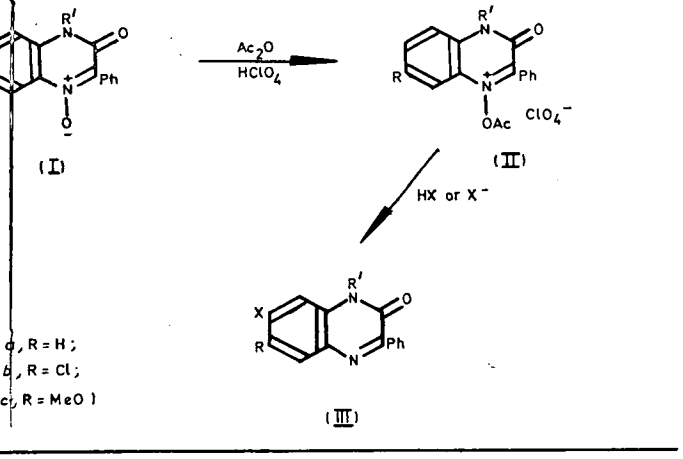
e substitution of the benzene nucleus observed in the ctions of 3,4–dihydro–3–oxo–2–phenylquinoxaline 1–*N*– des with acylating agents[1] is unusual in that the site of ack is not conjugated with the *N*–oxide centre. These ctions can be rationalised by a mechanism (see Scheme)



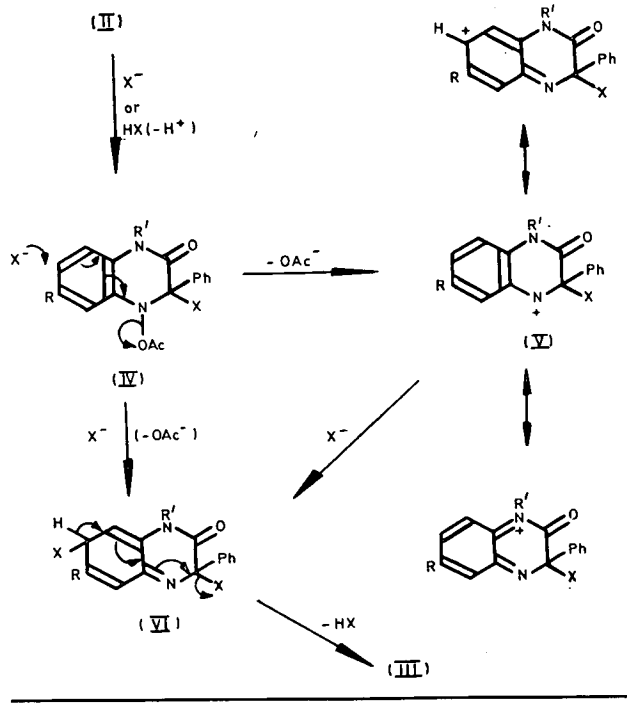
volving nucleophilic attack on *N*–acyloxy intermediates rived from initially formed *N*–acyloxyquinoxalinium salts. ese contentions are now supported by the novel substi- tion reactions undergone by *N*–acetoxyquinoxalinium rchlorates (II).*

Reaction of the 3,4–dihydro–3–oxo–2–phenylquinoxaline *N*–oxides (I*a–c*; R′ = H or Me) at room temperature with etic anhydride in the presence of perchloric acid gave high elds (80 – 96 per cent) of the yellow to red crystalline rchlorate salts (II*a–c*; R′ = H or Me), $\nu_{max.}$ 1835–1830 yclic $\overset{+}{N}\cdot OAc$) cm^{-1}, $\tau(CF_3\cdot CO_2H)$ 7·76 (3H, *s*, OAc). The l:s (II*a*; R′ = Me) and (II*c*; R′ = Me) tended to decompose pidly at room temperature, whereas the chloro-compound *b*; R′ = Me) and the NH-derivatives (II*a–c*; R′ = H) were latively stable.

atisfactory analyses and spectral data were obtained for all new mpounds.

The salt (II*b*; R′ = Me) underwent reaction at room temperature with ethereal suspensions of sodium acetate or lithium chloride to afford the quinoxalones (III*b*; R′ = Me, X = OAc) (83 per cent), mp 171°C and (III*b*; R′ = Me, X = Cl) (40 per cent), mp 171°C, whose structures are uniquely defined by the absence of *ortho* or *meta* splitting in the aromatic proton resonances in their ^1H n.m.r. spectra. These nucleophilic substitution reactions (and by implication

Scheme



the reactions of 3,4–dihydro–3–oxo–2–phenylquinoxaline 1–*N*–oxides with acetic anhydride[1] and acetyl chloride[1]) are explicable by a course (see Scheme) involving the initial formation of adducts (IV; X = OAc or Cl) and their conversion by synchronous attack by acetate or chloride ion and loss of the *N*–acetoxy leaving group into *para*-quinonoid

intermediates (VI) and thence by loss of HX into the observed products [(IV)→(VI)→(III)]. Alternatively, nucleophilic attack on the adducts (IV) is preceded by ionisation to resonance-stabilised nitrenium cation intermediates (V) [(IV)→(V)→(VI)→(III)]. Such intermediates have been invoked[2] to account for the substitution reactions of certain five-membered *N*–oxygenated benzaza heterocycles and those derived from quinoxalines [cf (V)] should show enhanced stability owing to the greater opportunity for resonance.

Nucleophilic substitution of the salts (II) is not confined to anions but also occurs readily with amines and with alcohols. Thus, the salts (II*a* and *b*; R′ = Me) underwent reaction with diethylamine in acetonitrile under reflux to afford moderate yields of the quinoxalones (III*a*; R′ = Me, X = Et_2N) (33 per cent), mp 153°C and (III*b*; R′ = Me, X = Et_2N) (45 per cent), mp 83°C. The salts (II*a* and *b*; R′ = H or Me) underwent reaction in general with hot methanol or ethanol to afford the corresponding 6–alkoxy–3,4–dihydro–3–oxo–2–phenylquinoxalines. Typical products and yields are shown in the Table. The failure of the strongly electron-donating methoxyl group in the salt (II*c*; R′ = H) to inhibit its conversion into the dimethoxyquinoxalone (III*c*; R′ = H, X = OMe) (see Table) demonstrates the facility of these reactio

Table **6-Alkoxy-3,4-dihydro-3-oxo-2-phenylquinoxalines**

Compound	Yield (per cent)	Mp(°C
(III*a*) R′ = H, X = OMe	73	240
(III*a*) R′ = Me, X = OEt	58	111
(III*b*) R′ = Me, X = OMe	77	188
(III*b*) R′ = H, X = OEt	57	279
(III*c*) R′ = H, X = OMe	50	255

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Synthesis and Reactivity of *N*-Hydroxybenzimidazolones

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Synthesis and Reactivity of *N*-Hydroxybenzimidazolones

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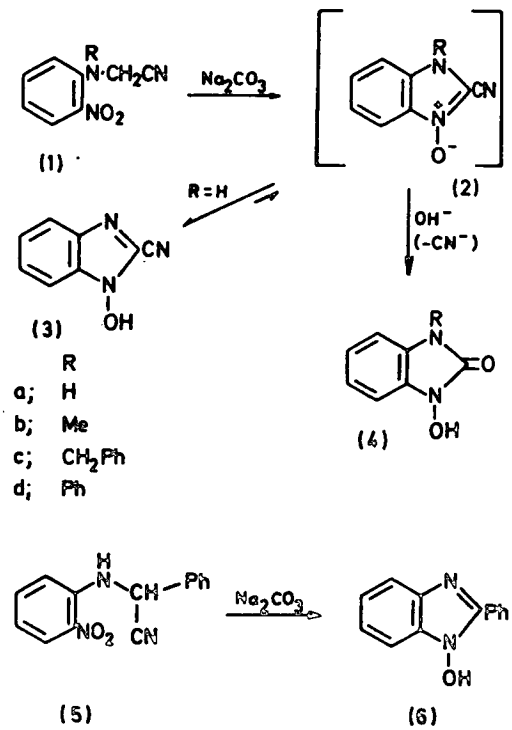
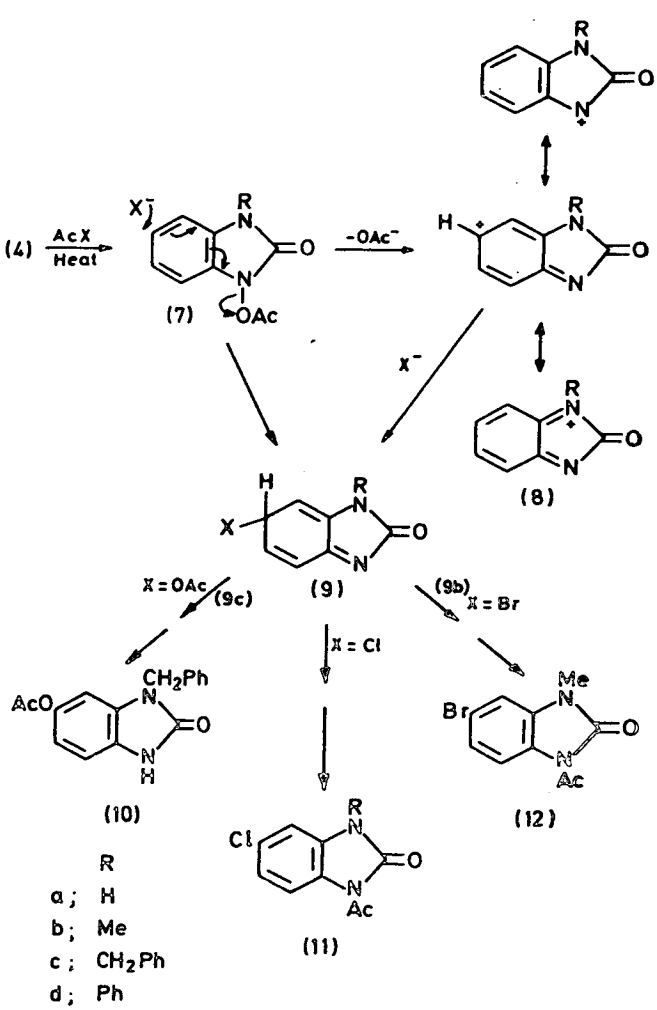
Summary Base-catalysed cyclisation of *N*-substituted 2-nitroanilinoacetonitriles affords *N*-hydroxybenzimidazolones which react with acylating agents to yield 5-substituted benzimidazolones.

FIVE-MEMBERED *N*-oxygenated benzaza-heterocycles are potential sources of heterocyclic nitrenium cations.[1] In this context, *N*-oxygenated benzimidazoles are of particular interest because in these substrates the second nitrogen atom should exert a stabilising effect on nitrenium ion formation. We now describe a general synthetic route to the *N*-hydroxybenzimidazolones (4) and their novel reactivity towards acylating agents.†



In a simple extension of previously reported[2] cyclisations, heating (**1a**)[3] with aqueous ethanolic sodium carbonate afforded the benzimidazole (**3**) (77%), m.p. 232°. The



† Satisfactory analysis and spectral data were obtained for all new compounds.

enyl derivative (**5**) cyclised to (**6**) (19%),[4] lending sup- to the mechanism suggested[5] for the cyanide-catalysed ation of (**6**) from benzylidene-2-nitroaniline. On the r hand, heating the *N*-substituted compounds (**1b—d**) aqueous ethanolic sodium carbonate gave good yields -75%) of the cyclic hydroxamic acids (**4b**),[6] m.p. 203°, m.p. 172°, and (**4d**), m.p. 216° which showed enhanced ity and gave characteristic green colours[7] with $FeCl_3$ in H. The formation of the *N*-hydroxybenzimidazolones ather than the *N*-oxides (**2**) in these reactions is in rd with the ready base-catalysed conversion of 2-cyano- ethylbenzimidazole 1-*N*-oxide (**2b**) into (**4b**).[6]

ne cyclic hydroxamic acids (**4**) reacted typically with ic anhydride at room temperature to afford the *N*- oxy-derivatives (**7**) (>90%) showing characteristically[7] carbonyl absorption at *ca.* 1800 $cm.^{-1}$ However, ylation at elevated temperature took a different course. acetic anhydride converted (**4c**) into the *C*-acetoxy- luct (**10**) (79%), m.p. 180°, while heating the *N*-hydroxy- imidazolones (**4b—d**) with acetyl chloride in glacial acetic acid afforded (70—80%) the corresponding 1-acetyl-5-chlorobenzimidazolones (**11b—d**). Hot acetyl bromide in glacial acetic acid converted the hydroxamic acid (**4b**) into the bromo-compound (**12**) (30%). The 5-position for the entering group in the products is supported by the splitting pattern of the aromatic proton resonances in their ^1H n.m.r. spectra.

The reactions of the *N*-hydroxybenzimidazolones with acylating agents at elevated temperatures are explicable in terms of nucleophilic attack on the *N*-acetoxy-intermediates (**7**) either concertedly with expulsion of the acetoxy-leaving group [(**7**) → (**9**) → (**10**)—(**12**)] or after ionisation to resonance stabilised nitrenium cations[1] [(**7**) → (**8**) → (**9**) → (**10**)—(**12**)] and subsequent acetylation.

We thank Drs. B. C. Cleere and B. K. Snell (Plant Protection Limited) for discussions and Plant Protection Limited for a maintenance award (to D.B.L.) and for financial support.

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